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Role of microRNAs in immunoregulatory functions of epithelial cells

Narjes Jafari[1] and Saeid Abediankenari[1,2*]

Abstract

Epithelial cells (ECs) provide the first line of defense against microbial threats and environmental challenges. They participate in the host's immune responses via the expression and secretion of various immune-related molecules such as cytokines and chemokines, as well as interaction with immune cells. A growing body of evidence suggests that the dysregulated function of ECs can be involved in the pathophysiology of a broad range of infectious, autoimmune, and inflammatory diseases, including inflammatory bowel disease (IBD), asthma, multiple sclerosis, and rheumatoid arthritis. To maintain a substantial immunoregulatory function of ECs, precise expression of different molecules and their regulatory effects are indispensable. MicroRNAs (miRNAs, miRs) are small non-coding RNAs that regulate gene expression commonly at post-transcriptional level through degradation of target messenger RNAs (mRNAs) or suppression of protein translation. MiRNAs implicate as critical regulators in many cellular processes, including apoptosis, growth, differentiation, and immune response. Due to the crucial roles of miRNAs in such a vast range of biological processes, they have become the spotlight of biological research for more than two decades, but we are still at the beginning stages of the use of miRNA-based therapies in the improvement of human health. Hence, in the present paper, attempts are made to provide a comprehensive overview with regard to the roles of miRNAs in the immunoregulatory functions of ECs. A better understanding of the molecular mechanisms through which immunoregulatory properties of ECs are manifested, could aid the development of efficient strategies to prevent and treat multiple human diseases.

Keywords MicroRNAs, Epithelial cells, Immune response, Immune regulation

Introduction

Epithelial cells (ECs) such as those in lining the skin, gastrointestinal tract, respiratory tract, and oral cavity provide the first line of host defense against foreign bodies and injury [1]. In addition to their role in creating a physical barrier, ECs are critical in the recruitment of immune cells to the affected site and contribute either independently or in collaboration with resident/recruited immune cells to provide epithelial tissue immunity [2, 3]. To perform these functions, ECs express a wide range of biomolecules associated with the immune response, including cytokines, chemokines, co-stimulatory molecules, and major histocompatibility complex (MHC) class I and II. Moreover, ECs are equipped with pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) which enable them to recognize distinct pathogen-associated molecular patterns (PAMPs) and to participate in the initiation of appropriate immune responses against microbial pathogens [2, 3]. Different gene products regulate the EC functions. Addressing these molecules and their associated pathways will provide new perspectives to understanding malignant diseases related to the dysfunction of ECs.

*Correspondence:
Saeid Abediankenari
abedianlab@yahoo.co.uk
[1] Immunogenetics Research Center, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran
[2] Department of Immunology, Faculty of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

MicroRNAs (miRNAs, miRs) are a class of small non-coding RNAs that regulate gene expression at the post-transcriptional level mainly through degradation or translational repression of target mRNAs. MiRNAs play important roles in various cellular processes including development, differentiation, apoptosis, and immune response [4–6]. Furthermore, there are growing evidence concerning the contribution of miRNAs in the regulation of almost all aspects of EC functions such as renewal and wound healing [7–9], epithelial/endothelial barrier maintenance [10, 11], response to oxidative stress [12, 13], autophagy [14] and epithelial immunity [15, 16]. Also, previous studies have explored that dysregulation of miRNAs in ECs is associated with several immune-related disorders such as inflammatory bowel disease (IBD) [11, 17], and asthma [18]. Therefore, in this review, our main focus is directed toward miRNA involvement in the regulation of immune response by ECs. As well, we summarize multiple extracellular roles of miRNA in mediating epithelial-immune cell communications. Of note, we provide an overview of the current knowledge about the miRNA regulatory effects in the modulation of EC function in confronting COVID-19 infection.

Better understanding of the immunoregulatory features of ECs and the mediators that play a fundamental role in which, will guide future research to design efficient therapeutic interventions against various infectious and inflammatory diseases.

Epithelial cell functions: from physical/biochemical barrier to immune protection

The ECs protect the host with the formation of a physical and biochemical barrier separating the host body from the external environment. In addition, the ECs can respond to danger signals such as microbial stimuli and contribute to the regulation of both tolerogenic and immunogenic responses [19]. Given the important role of ECs in the establishment of protective immunity, disruption of EC homeostasis creates the risk of infection and inflammatory disorders.

Tight junction proteins (TJPs), production of mucous layer, secretion of broadly targeted antimicrobial proteins (AMPs), and transcytosis of secretory immunoglobulin A (SIgA) are among the main mechanisms that contribute to the protective function of the epithelial barrier [19]. Also, the epithelium can respond to pathogens by secretion of various cytokines responsible for recruiting immune cells to infected or injured sites [20].

In the following paragraphs, we briefly discuss evidence about the protective mechanisms by which the epithelium improves host defense against invading pathogens.

Role of TJPs in epithelial barrier function

The ECs are joined by tight junctions. TJPs, located at the tight junctions, comprise transmembrane (or integral membrane) proteins (such as junctional adhesion molecules (JAMs), tricellulin, claudins, and occludin) and peripherally associated scaffolding proteins (such as ZO (zonula occludens)-1, -2 and -3). These proteins determine the mucosal permeability and regulate the transport of solutes, ions, and water through the paracellular pathway of ECs [21–23]. Several lines of evidence demonstrate the importance of TJPs in the regulation of epithelium function and prevention of severe inflammatory responses. For instance, Yuki et al. reported that levels of ZO-1 and claudin-1 proteins were decreased in the skin of patients with atopic dermatitis [24]. In another study, Krug et al. reported that tricellulin, a protein that participates in organization of tricellular as well as bicellular tight junctions [21], was decreased in patients with ulcerative colitis, and its reduction increased the paracellular passage of macromolecule [25].

Expression of AMPs as a potent arm of the innate immune system in the epithelial barrier

AMPs are charged peptides that act as a protective part of the host̕s innate immune system against a broad range of bacteria, fungi, and viruses. For example, cathelicidins—— an important group of cationic AMPs—— convert into their mature form (LL-37 in humans and mCRAMP in mice [26]) through extracellular cleavage by proteinase-3 [27]. The AMP LL-37 is produced by various human cell types such as neutrophils [26], mast cells [28], monocytes [29], and ECs from different organs including intestine [30], gastric [31], lung [32, 33] and mouth [34]. This AMP showed antimicrobial activity against a variety of pathogens such as *Pseudomonas aeruginosa* [27, 35], *Helicobacter pylori* [31], *Staphylococcus aureus* [36, 37], *Candida albicans* [34], and respiratory syncytial virus (RSV) [38]. Besides direct antimicrobial activity [38, 39], LL37 shows diverse immunoregulatory functions against infection. Wang et al., reported that LL37 enhances bacterial phagocytosis in human macrophages. Furthermore, the expression of Fcγ receptors (including CD32 and CD64), TLR4, and CD14 was increased on LL-37-treated macrophages [40]. Treatment with LL-37 significantly enhanced interleukin (IL)-6 and IL-8 release from human bronchial epithelial IB3-1 cells [27]. As such, Neumann et al., found a role for LL-37 in the formation of neutrophil extracellular traps [41]. In addition, another study reported that mouse and human cathelicidins released by neutrophils promoted differentiation and survival of Th17 cells, and directed subsequent adaptive immune responses through which [26]. As an example of the pathophysiological role of LL-37 in disease progression, Jiao et al. study provided evidence that elevated levels of LL-37 induced asthma exacerbation through the activation of eosinophils interacting with bronchial ECs in inflammatory airway [42]. This evidence and other similar findings indicate that AMPs such as LL37 mediate communications between the ECs and immune cells.

Other AMPs such as defensins, are also produced by ECs and protect the host against pathogens [43], however, providing a comprehensive overview with regard to different types of AMPs is beyond the scope of the present article.

Secretion of IgA and immunity in epithelial barrier

Secretory IgA (SIgA) is the predominant antibody isotype on mucosal surfaces of humans and many other mammals which plays important roles in protection against pathogens without leading to inflammation because of its inability to activate the complement pathway [44]. In addition, the production of SIgA regulates the commensal microbiota composition to maintain a healthy balance between the host and the microorganisms [44, 45].

IgA-producing plasma cells abundantly reside within the lamina propria of the gastrointestinal tract, but a significant number of these cells are also found in the other mucosal sites such as upper and lower airways [44] and genital tract [46]. The multimeric IgA produced by local plasma cells in the lamina propria is transported across the ECs —— which express poly-Ig receptor (pIgR) on their basolateral surfaces—— into the mucosal lumen [44, 45]. Moreover, IgA-producing plasma cells are also present within non-mucosal sites such as in the mammary gland [47], bone marrow [48], and brain tissue [49], although data suggests that systematic and mucosal IgA producing plasma cells are of the same origin [47–49].

The major part of mucosal IgA-secreting plasma cells is derived from activated B-cells in mucosal-associated lymphoid tissues (MALT). The majority of MALT is localized along the gut, termed as gut-associated lymphoid tissues (GALT). The GALT includes several structures which the Peyer's patches (PPs) are the main IgA-inductive sites among them [45]. Activated naïve IgM B cells in the gut differentiate into IgA-secreting plasma cells by class-switch recombination (CSR) from Cμ to Cα in the constant region of the Ig heavy chain. This process is dependent on priming by mucosal dendritic cells (DCs) carrying various antigens and live bacteria from the luminal surface into the PPs [19, 45, 50].

Briefly, in the presence of cognate CD4+T cells, interaction between CD40 on the surface of B cells and its ligand (CD40L) on T cells as well as secretion of multiple cytokines lead to high-affinity antigen-specific IgA production to neutralize the pathogens [19, 45, 51]. In addition, in the absence of T cells, CSR to IgA could occur through the stimulation of B cells by APRIL (A proliferation-inducing ligand) and BAFF (B-cell activating factor of the TNF family) [19, 51], which their structure and function are related to CD40L [52]. A role is also known for APRIL and BAFF in support of survival of IgA+B cells and IgA-producing plasma cells [45, 50, 52]. In response to commensal bacteria, the production of APRIL and BAFF by ECs directly stimulates the B cells and triggers IgA CSR. Furthermore, ECs induce the production of APRIL and BAFF by mucosal DCs which intensify the effect on B cell stimulation [19, 52]. However, there are several other important factors influencing IgA CSR which were well discussed in previous studies [45, 50].

Expression of immunoregulatory molecules by ECs and interaction with immune cells

It is noteworthy that epithelial tissues contain a complex network of resident immune cells that play crucial roles in host defense and tissue homeostasis. Tissue-resident immune cells are both myeloid and lymphoid cell subsets mainly including mononuclear phagocytes, innate lymphoid cells, tissue-resident T cells, and IgA-secreting plasma cells [19, 53]. In response to a challenge, such as invading pathogens and tissue injury, ECs exert their influence on priming of immune responses via communications with immune cells resident in the tissue and those that are infiltrated from the periphery to resolve the challenge, hence, restore the tissue to its original condition [53].

The production and secretion of numerous immunoregulatory signals by ECs such as transforming growth factor-β (TGF-β) [54, 55], IL-8 [20, 55], thymic stromal lymphopoietin (TSLP) [55, 56], IL-25 [57, 58] and many other biomolecules provide possible tools for the translation of stimuli-derived signals from ECs to immune cells and promote cross-talk between them. We summarized several biomolecules secreted by ECs as well as their immune-related functions in Table 1. In the following, several regulatory interactions of ECs in the immune system are mentioned.

Previous data showed that human corneal ECs can internalize *Aspergillus flavus* spores via actin-mediated endocytosis [94] and differentially express distinct sets of gene transcripts associated with tumor necrosis factor (TNF) signaling, Th17 differentiation, NF-κB signaling, chemokine signaling and B cell receptor signaling against fungal infection compared to control [95]. After stimulation with killed *Aspergillus fumigatus*, pro-inflammatory cytokines such as CXCL1, TNF-α, and IL-6 and activation of P38 MAPK were induced through LOX-1 (lectin-like oxidized

Table 1 Immune-regulatory mediators secreted by epithelial cells

Factors	Epithelial cell type	Function	References
IL-8	Cornea, Intestine, Caco2 cells, T84 cells, HeLa cells, Bronchus, A549 cells, HaCaT cells, NHEKs, Mouse skin, Goat mammary, Colon, IB3-1 cells, Human skin and gingival keratinocytes	- Chemoattraction and activation of polymorphonuclear leukocytes, including neutrophils and basophils -Angiogenesis	[20, 27, 55, 57, 59–67]
IL-6	Caco-2 cells, A549 cells, HaCaT cells, NHEKs, Mouse skin, IB3-1 cells, Human and rat corneas	- Involved in both pro-inflammatory and anti-inflammatory responses [68]	[20, 27, 59, 65, 69–71]
IL-1β	Caco-2 cells, Skin of psoriatic patients, Human keratinocyte, HaCaT cells, NHEKs, Mouse skin, Goat mammary, Human cornea	- Inflammatory cytokine - Induction of insulin resistance in human keratinocytes via p38MAPK (mitogen-activated protein kinase), which blocks insulin-dependent differentiation of these cells - Proliferation of keratinocytes	[59, 66, 71–73]
TNF-α	Caco-2 cells, A549 cells, Mouse skin, Human keratinocyte, Human and rat cornea	- Inflammatory cytokine	[20, 59, 61, 65, 69, 71]
IL-1α	A549 cells	- Inflammatory cytokine	[65]
IFN-β	A549 cells	- Inflammatory cytokine	[65, 70]
IL-12	A549 cells	- Inflammatory cytokine	[20, 65]
IL-10	A549 cells, Human cornea	- Anti-inflammatory cytokine	[20, 73]
IL-13	A549 cells	- Anti-inflammatory cytokine	[20]
IL-17	A549 cells	-A pro-inflammatory cytokine which may contribute to the recruitment of the immune cells such as neutrophils	[20]
M-CSF	HT29 cells, Intestine	- A pro-inflammatory cytokine - Serves as a chemoattractant which recruits macrophages to the infection site and activates them to phagocytose and kill foreign microorganisms	[74]
G-CSF	A549 cells	- Acts as an anti-inflammatory cytokine [75] - Exerts pivotal regulatory effects in hematopoiesis and immune responses [76] - Prevents overactivation of monocytes and lymphocytes by reducing the release of pro-inflammatory mediators and concomitantly activating the anti-inflammatory defense of neutrophils [75] - Stimulates granulocyte production, maturation, and migration to the infection site [20, 76] - Promotes T cell tolerance in pathological conditions associated with a Th1/Th2 imbalance [76]	[20]
GM-CSF	A549 cells	- A hematopoietic growth factor that induces the generation of granulocyte and macrophage populations from precursor cells [77, 78] - Promotes the survival, activation, and migration of macrophages, neutrophils, and eosinophils, as well as DC differentiation and maturation [20, 77] - Acts as an immune-modulatory cytokine which has a pivotal role in regulating the immune response and maintaining immunological tolerance [78]	[20]
IFN-γ	A549 cells	- Pro-inflammatory cytokine	[20]

Table 1 (continued)

Factors	Epithelial cell type	Function	References
TSLP	Intestine, Caco2 cells,, Skin	- An IL-7-like cytokine that acts as a key mediator of epithelial cell–T cell crosstalk - In co-operation with other mediators such as TGF-β, induces the DCs and macrophages with tolerogenic properties - Promotes Th2 cell differentiation and activation while repressing the Th1 arm - Induces ILC2 in the skin	[55, 56, 79, 80]
RELMβ	Intestine	- A goblet cell-specific effector whose expression is mainly induced by the Th2 antiparasitic cytokine (IL-13)-dependent response in the intestine	[79]
CCL20 (MIP-3α)	Human keratinocyte, Colon	- A chemotactic cytokine that induces the migration of cells such as DC and lymphocytes and plays an important role at skin and mucosal surfaces under homeostatic or inflammatory conditions [81]	[61, 67]
IL-25 (IL-17E)	Tuft cells, Bronchus, Nose, Lung, Keratinocyte	- An alarming molecule which can be released extracellularly by cellular damage - Enhances Th2 cell differentiation and Th2 cell-mediated immune responses by inducing the expression of its cytokines, such as IL-4, IL-5, and IL-13 - Stimulates ILC2 to produce cytokines (such as IL-4 and IL-13) in response to helminth and skin challenge - Promotes eosinophilic inflammation and plays roles in the development of allergen-induced disorders - Induces keratinocyte proliferation and production of inflammatory cytokines [82]	[57, 80, 82–84]
IL-33[a]	Keratinocytes, Bronchus, Skin	- A potent stimulus for the activation and migration of skin-derived ILC2s - Induces a Th2- type immune response	[57, 80, 85]
TGF-β	Intestine, Caco2 cells	- In co-operation with other mediators such as TSLP, implicates in the differentiation of tolerogenic DC and macrophage in response to commensal bacteria-derived stimuli	[55]
IL-7	Intestine, A549 cells	- A major survival factor for mature T cells - Promotes the development and homeostasis of T cells, B cells, ILCs, and macrophages - Induces proliferation of naive and memory T cells and enhances effector T cell responses, preferentially Th1 and Th17 responses - Regulates the homeostasis of intestinal ECs, colon function, and the composition of the commensal microflora - Contributes to early immune activation in response to enteric bacterial infection	[20, 86, 87]
APRIL (TNFSF13)	Intestine, Primary keratinocytes, HaCaT cells, normal renal tissue, renal cell carcinomas, HepG2 and Hep3B cells, hepatocellular carcinoma (HCC) tissue, normal liver	- Is involved in B lymphocyte development, proliferation, and differentiation [88, 89] - Is required for immunoglobulin class switch recombination in B cells [90] - Promotes the development and progression of various cancer cell lines and tumors [89, 91]; but suppression the proliferation of HCC cell lines (HepG2 and Hep3B) by that was also reported [88]	[88–90, 92]

Table 1 (continued)

Factors	Epithelial cell type	Function	References
BAFF (TNFSF13B)	Intestine, Primary keratinocytes, HaCaT cells, normal renal tissue, renal cell carcinomas, HepG2 and Hep3B cells, HCC tissue, normal liver	- Induces immunoglobulin (IgA1 and, to some extent, IgA2) class switch recombination in B cells [90] - Involved in B lymphocyte proliferation, differentiation [88], and survival [91]	[88–90, 92]
MIP-2α (CXCL2)	Human colon	- Chemotactic cytokine	[67]
MIP-1α	A549 cells	- Chemotactic chemokine	[20]
MCP-1 (CCL2)	HaCaT cells, NHEKs, Mouse skin, Human colon; A549 cells	- Pro-inflammatory cytokine - Recruits monocytes, T cells, and dendritic cells [82] - Regulates cell proliferation and cell-cycle progression [82]	[20, 59, 67]
CCL4	Goat mammary	- Inflammatory response - Chemotaxis	[66]
CXCL1 (GRO1)	HaCaT cells, Human colon, Human and rat cornea, Human skin and gingival keratinocytes	- A member of the CXC chemokine subfamily - Involved in chemoattraction of neutrophils [93]	[59, 60, 67, 69]

Abbreviation: IL Interleukin, *TNF-α* Tumor necrosis factor-α, *IFN-β* Interferon-β, *M-CSF* Macrophage colony-stimulating factor, *G-CSF* Granulocyte colony-stimulating factor, *GM-CSF* Granulocyte–macrophage colony-stimulating factor, *IFN-γ* Interferon-γ, *TSLP* Thymic stromal lymphopoietin, *Th2* T helper type 2, *Th1* T helper type 1, *ILC2* Type 2 innate lymphoid cell; *RELMβ* Resistin-like molecule β, *MIP-3α* Macrophage inflammatory peptide-3α, *DC* Dendritic cell, *TGF-β* Transforming growth factor-β, *APRIL* A proliferation-inducing ligand, *BAFF* B cell-activating factor, *MIP-2α* Macrophage inflammatory peptide-2α, *MIP-1α* Macrophage inflammatory protein-1α, *MCP-1* Monocyte chemoattractant protein, *CCL4* Chemokine C–C motif ligand 4, *GRO1* Growth-related oncogene-alpha

Cells**:** *Caco-2* human colon cancer cell line, *T84* human colon adenocarcinoma cell line, *HeLa* human cervical cancer cell line, *A549* human pulmonary epithelial cell line, *HaCaT* Human keratinocyte cell line, *NHEK*s primary normal human epidermal keratinocytes, *IB3-1* human cystic fibrosis bronchial epithelial cells, *HT29* human colon adenocarcinoma cell line, *Tuft cells* a rare epithelial cell type in the intestinal epithelium, *HepG2* human hepatocellular carcinoma; *Hep3B* human hepatocellular carcinoma

[a] IL-33 is a nuclear protein that accumulates in the cell nucleus upon synthesis. Non-restored cell damage or necrotic cell death mediates the extracellular release of stored IL-33 [57, 85]

low-density lipoprotein receptor 1) in rat corneal ECs. Also, the expression of CXCL1 and TNF-α was found to be elevated through LOX-1 in human corneal ECs [69]. Moreover, corneal ECs upregulated the expression of dectin-1 [96], TLR-2, TLR-4, IL-1β, and IL-10 upon stimulation with *A. fumigatus* antigens [97].

Pulmonary ECs infected with different strains of *Mycobacterium tuberculosis* at early stage can produce a wide range of cytokines, chemokines, growth factors and PRRs such as IL-6, IL-8, interferon (IFN)-γ, TNF-α, granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), TLR3, TLR5, and TLR2 [20].

Keratinocytes are the main cell type of the epidermis—— the outermost layer of skin —— which in addition to providing a physical barrier, can express different types of cytokine receptors and PRRs such as TLRs, nucleotide-binding oligomerization domain-like receptors (NLRs), and RIG-I–like receptors (RLRs). Furthermore, they produce a wide variety of cytokines, chemokines, growth factors as well as AMPs [98]. For example, human keratinocytes and mouse skin produce inflammatory mediators IL-6, IL-1β, IL-8, cyclooxygenase (COX)-2, and monocyte chemoattractant protein (MCP-1) mediated by NF-κB signaling in response to ultraviolet B (UVB) irradiation [59]. Under the mediation of IL-25, keratinocytes can produce pro-inflammatory cytokines and chemokines via activation of the STAT3 pathway in a murine psoriasis model—— a chronic autoinflammatory skin disease—— indicating that keratinocytes play a critical role in the pathogenesis of this disease [82].

The luminal surface of PPs is covered by the follicle-associated epithelium (FAE) which contains relatively limited numbers of goblet cells, enteroendocrine cells, and intraepithelial lymphocytes and is rich in specialized ECs known as microfold cells (M cells). M cells, which are phagocytic, constantly sample and transport luminal antigens to the underlying GALT. Then, M cells release their transcytosed material within intraepithelial pockets formed by their expanded basolateral side. Within these pockets, M cells interact directly with the immune cells residing in the subepithelial dome (SED) beneath the FAE. The antigens transported by M cells are then taken up by antigen-presenting cells (APCs) residing in the SED such as immature DCs. The antigen-primed DCs undergo a maturation process and migrate to the T-cell zone of GALT to present antigens to T cells, leading to the activation of antigen-specific B cells and ultimately the induction of mucosal immune responses including the production of IgA antibodies by lamina propria plasma cells [16, 99, 100].

ECs act as non-professional phagocytes

As mentioned in the above section, ECs are capable of phagocytosis and elimination of cell debris, dead cells, and invading pathogens [101, 102]. However, they use different phagocytosis mechanisms compared to professional phagocytes such as macrophages. Although ECs have a remarkably lower phagocytic efficiency compared to professional phagocytes, accumulating evidence indicates that their phagocytic activity has a significant contribution in maintaining tissue homeostasis as well as in eliciting an adequate innate immune response against pathogens [101].

Capasso et al. study showed that *Pseudomonas aeruginosa* was attached to apoptotic ECs or apoptotic bodies and internalized by surrounding ECs via efferocytosis—— a mechanism in which phagocytes engulf and remove apoptotic cells. Finally, the bacteria were killed within the cells through lysosomal processes [103].

ECs act as non-professional antigen-presenting cells

In addition to acting as non-professional phagocytes, ECs can present different antigens by major histocompatibility complex (MHC) class I and MHC class II molecules to the intraepithelial lymphocytes—— primarily a heterogeneous T cell population including conventional T cell, γδ T cell, NKT cell, CD4+CD8αα+double-positive T cell [19, 104] —— and lamina propria lymphocytes [105, 106]. Thus, ECs have the potential to act as non-professional APCs and stimulate immune responses against numerous antigens [105, 106].

MHC- I molecules are expressed by most nucleated cells and mainly present endogenous antigens to cytotoxic CD8+T lymphocytes. While, MHC- II molecules are predominantly expressed on the professional APCs (DCs, B cells, macrophages) and thymic epithelia, and primarily present antigens to CD4+T cells [107]. However, evidence shows that MHC-II proteins and associated processing molecules are also expressed by non-hematopoietic cells, such as fibroblasts, myofibroblasts, lymphatic endothelial cells, and ECs [102, 106, 108–111] which provide an important prerequisite for them to function as non-conventional APCs [112]. Although numerous studies reported the role of IFN-γ as a critical inducer of MHC- II expression by ECs [102, 113, 114], limited evidence shows that there are potential IFN-γ independent mechanisms in the induction of MHC- II expression on ECs [115]. Despite the expression of MHC- II molecules on the surface of ECs being reported in both normal and inflammatory conditions, their expression level can be different between health and pathological conditions. For example, an elevated level of MHC-II expression was found in IBD and Epstein-Barr virus (EBV)-associated gastric cancer compared to the normal groups [113, 116].

In the context of antigen presentation through MHC-II by ECs, either immune-enhancing or immunosuppressive responses have been suggested. Several studies reported the upregulated expression of MHC-II by ECs under inflammatory conditions which activated effector CD4+T cell responses [117, 118]. While, other studies reported conflicting findings and suggested a tolerogenic role of antigen presentation by ECs through regulatory T (Treg) cell expansion [119, 120]. These contradictory observations highlight the need for further investigations to illustrate the exact outcome of antigen presentation by ECs to effector or regulatory CD4+T cells. The findings mentioned below support the ability of ECs for activation of T cells through antigen presentation.

Shenoy et al. study showed that antigen presentation by lung ECs critically regulated CD4+resident memory T (T_{RM}) cell function and reported an important role of epithelial CD4+T_{RM} cell immune interactions in establishing barrier immunity [106]. Koyama et al. found that MHC-II-expressing intestinal ECs have a pivotal role in alloantigen presentation to donor CD4+T cells in vivo and thereby in the initiation of acute lethal graft-versus-host disease (GVHD)—— an immunopathology mediated by mature donor T cells which recognize host alloantigens and leads to severe inflammation —— following allogeneic bone marrow transplantation. They also reported that intestinal EC-specific deletion of MHC-II abrogated lethal GVHD in the gastrointestinal tract [118].

Hatano et al. reported that antigen presentation by IFN-γ- pretreated murine small intestinal ECs induced antigen-specific proliferation in CD4+intestinal intraepithelial lymphocytes (IILs) and enhanced IFN-γ secretion by these cells [105]. As another example, Dotan et al. reported that co-culture of intestinal ECs isolated from IBD patients with autologous or allogeneic healthy peripheral blood T cells stimulated the proliferation and IFN-γ secretion in CD4+T cells which were significantly greater degree than those in T cells stimulated with normal intestinal ECs. Moreover, blockade of MHC-II (DR) harnessed CD4+T cell proliferation and the IFN-γ secretion in IBD intestinal EC- CD4+T cell co-cultures, with a lesser effect in the normal intestinal EC- CD4+T cell co-cultures [117].

About the extensive capabilities of ECs, in the above section, we attempted to provide a short overview of the manifold functions of these cells in immune defense which should be given more attention in future studies.

MiRNAs and epithelial immune responses

Accumulating data indicates that miRNAs play key roles in determining the fate and modulation of functions of ECs, such as proliferation [121], differentiation [16, 79], apoptosis, and autophagy [122] through targeting different genes and signaling pathways. Nakato et al., with the generation of mice harboring intestinal EC- specific deletion of Dicer1, found that intestinal epithelial miRNAs (miRNAs in FAE) play a significant role in the differentiation and function of M cells and contribute to mucosal immune homeostasis [16].

MiRNAs affect the epithelial and endothelial permeability through the regulation of TJP expression. For example, miR-122a, miR-144, and miR-200C-3p can increase intestinal tight junction permeability by directly targeting and degradation of the occludin mRNA [123–125]. MiR-29 can increase intestinal epithelial permeability by directly targeting and reduction of the claudin-1 mRNA [126]. MiR-144 promotes intestinal permeability by directly targeting ZO1 mRNA [123] (Fig. 1). Also, miR-21-5p increases intestinal epithelial permeability via induction of ARF4 (ADP ribosylation factor 4) expression (ARF4 is not a direct target of this miRNA) [127]. Dysregulation of epithelial barrier function contributes to a broad range of autoimmune and inflammatory diseases [11, 124].

Moreover, epithelium-expressed miRNAs act as mediators for crosstalk between ECs and the immune system (Fig. 1). Biotin et al. study, using a mouse model of inactivated Dicer1 in the gut, showed that epithelial miRNAs play a fundamental role in the induction of the anti-parasitic Th2 (T helper type 2) responses and modulation of gut mucosal immunity. Particularly, they showed that miR-375 expression in mouse colonic epithelium induced higher expression of RELMβ and TSLP—— two epithelium-derived cytokines that regulate mucosal anti-parasitic Th2 response [79].

Kawasaki et al. found that miR-429 exerts anti-inflammatory function through the suppression of inflammatory cytokines such as IL-8 by inhibiting the NF-κB pathway in gingival EC line (squamous cell carcinoma Ca9-22 cells) [15]. In Chen et al. study, stable knockdown (KD) gingival EC lines for several epithelium-expressed miRNAs were constructed and their inflammatory response to infection with periodontal pathogens was assessed. They reported that pathogen-stimulated miR-126 KD cells produced lower IL-8 and CXCL1 levels than wild-type cells. In contrast, infection of miR-155 KD and miR-210 KD cells showed higher IL-8 and CXCL1 expression than wild-type cells [60].

In the irradiated mouse model, oral gavage with hydrogen-water increased the miR-1968-5p level in the small intestine. MiR-1968-5p directly targeted and

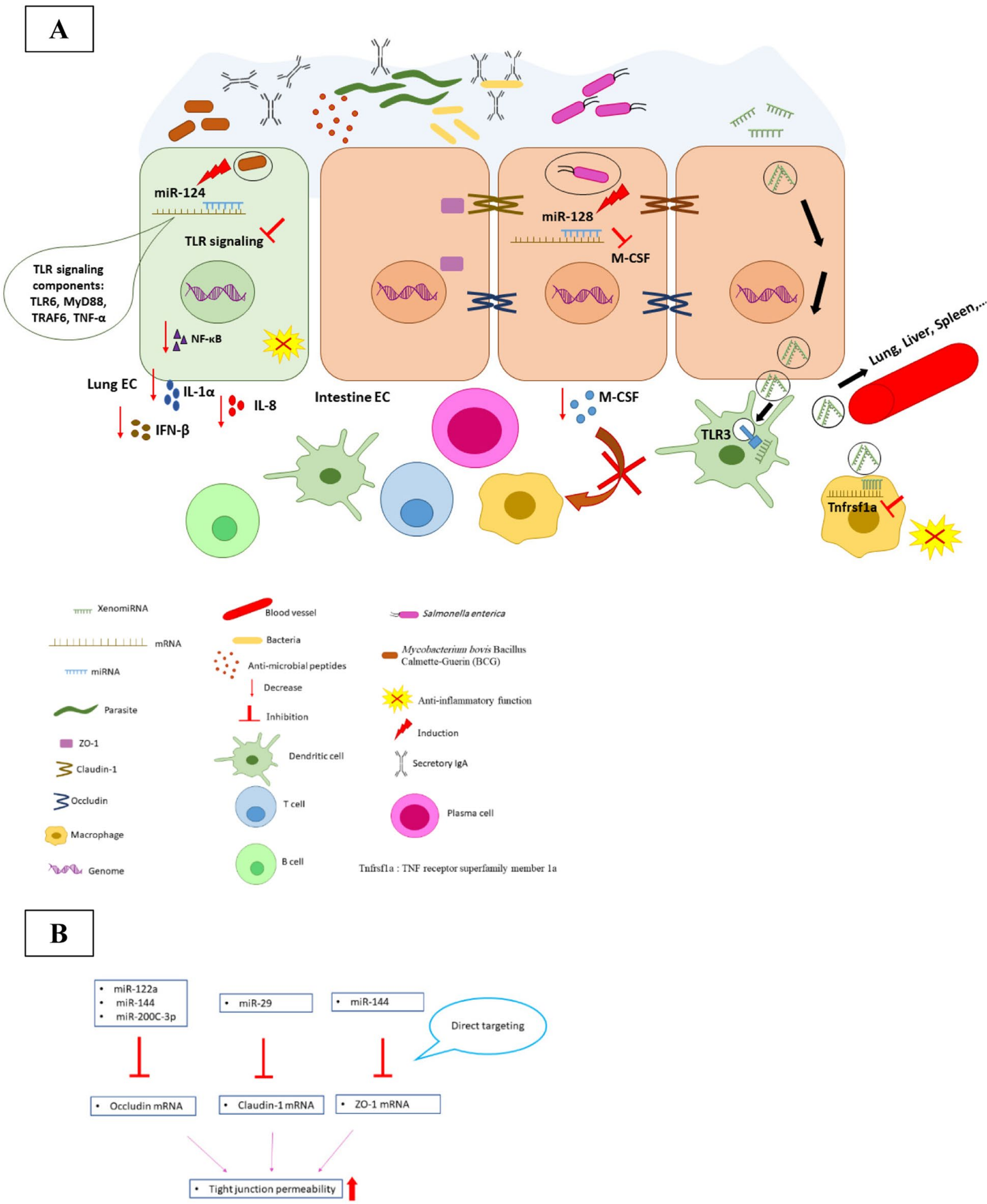

Fig. 1 Schematic drawing that briefly illustrates (**A**) the microRNA involvement in the modulation of immune response by epithelial cells; and (**B**) the effect of microRNAs in epithelial permeability through the regulation of tight junction protein expression

downregulated the MyD88 (myeloid differentiation factor 88) expression and alleviated the intestinal injury induced by irradiation [128]. It is worth noting that MyD88 was known as a key player in inflammatory signaling pathways downstream of IL-1 receptor (IL-1R) families and mammalian TLRs [129]. A study on the function of miR-146a in keratinocytes identified this miRNA as a regulatory agent in keratinocyte innate immunity in which TLR2- induced miR-146a acted as a negative feedback regulator via suppression of the inflammatory mediators such as IL-8, CCL20, and TNF-α. In addition, the study showed that miR-146a repressed the chemotactic attraction of neutrophils by keratinocytes [61]. As well, the Li et al. study reported that miRNA-23a-enriched exosomes from hypoxic tubular ECs mediated the cross-talk between these cells and macrophages to promote renal tubulointerstitial inflammation [130]. Thus, the blockade of miRNA transfer between ECs and immune cells may act as a potential therapeutic approach to ameliorate an immune-related disorder. Further findings concerning the role of miRNAs in the regulation of immune-related target genes expressed in ECs were presented in Table 2.

Role of EC miRNAs in the control of microbial infections

The role of miRNAs in the interactions of the epithelium with the microbial pathogen has been widely investigated [151–153]. In this context, accumulating data reported that miRNA-mediated immune responses are involved in either pathogen survival or pathogen elimination. Several examples are mentioned as follows.

Upon influenza A virus infection, miR-136 is up-regulated in A549 human lung ECs. Subsequently, this miRNA mediates the up-regulation of several cytokines including IL-6 and IFN-β, and stimulates innate immunity by acting as a ligand for RIG-I (retinoic acid-inducible gene 1) leading to suppression of virus replication [70]. On the other hand, influenza A virus downregulates miR-17-3p and miR-221 in human lung ECs during the early-stage infection which this causes enhanced viral replication possibly through GALNT3 (GalNAc transferase 3) upregulation [154].

Aguilar et al. indicated that *Salmonella typhimurium* infection induced changes in the miRnome expression via downregulation of transcription factor E2F1. These changes promoted *Salmonella* replication in both infected epithelial and bystander cells [151]. Yang K et al. demonstrated that after *Pseudomonas aeruginosa* infection, miR-155 expression was upregulated in human and mouse corneas and was predominantly expressed in macrophages. Moreover, they found that miR-155 reduced the macrophage-mediated elimination of *P. aeruginosa* by targeting Rheb (Ras homolog enriched in the brain), and therefore, involved in corneal susceptibility to *P. aeruginosa* keratitis [155]. Another study indicated that *Salmonella enterica* infection increased miR-128 expression in intestinal ECs which, in turn, decreased the levels of EC-secreted M-CSF (macrophage colony-stimulating factor), leading to impaired M-CSF–mediated macrophage recruitment. It is noteworthy that M-CSF was confirmed as a direct target of miR-128 [74].

Recently, several studies have reported the possible roles of host miRNAs to serve as anti- or pro-viral effectors among COVID-19 patients and provided new perspectives to develop preventive and treatment strategies based on miRNAs. For example, Lu D et al. reported that miR-200c can directly target and inhibit the expression of angiotensin-converting enzyme 2 (ACE2) —— known as a receptor for the spike protein of SARS-CoV-2 which plays fundamental roles during the COVID-19 infection—— in cardiomyocytes [156]. Given that ACE2 is remarkably expressed in different tissues including the lung, heart, kidney, intestine, liver, testis, and central nervous system [156, 157], miR-200c could be an interesting topic for future research to design a potential strategy for prevention and treatment of complications during the COVID-19 infection.

According to a few studies, several viruses use the "miRNA sponge effect" to disrupt the pathways regulated by host miRNAs. Through this mechanism, the viral genome acts as miRNA sponges that competitively interact with host miRNAs to deplete specific miRNAs and cause the disruption of miRNA/natural target interactions [158, 159]. For example, a recent study reported that hsa-miR-302c-5p—— a key regulator of ACE2—— can be sponged by the SARS-CoV-2 genome. This effect potentially led to an elevated expression of ACE2 [158] which was found to be associated with severe COVID-19 disease [160]. Therefore, focusing attention on such studies could be helpful to explore the exact role of miRNAs in the regulation of EC immune responses to microbial infection and may provide a promising target for clinical treatment of infectious diseases.

A brief overview of several studies reporting miRNAs expressed in EC and their respective function in the immune system and immune disorders is presented in Table 3.

Xeno-miRNAs and effects on immune system

Growing evidence points to certain subtypes of miRNAs which are codified by non-host genomes but are present in body fluids and tissues of different species of animals, including humans. They have been termed xeno-miRNA (xeno-miRs) which can modulate gene expression among various species and kingdoms. Xeno-miRs in humans have been reported from numerous exogenous sources,

Table 2 Immune-related miRNAs and their direct target genes expressed in epithelial cells (ECs). MiRNAs directly target the mentioned genes and downregulate their expression and functions

miRNA	Direct target gene: Function	Epithelial cell type	References
miR-128	**M-CSF**: A pro-inflammatory cytokine that recruits macrophages to the infection site and promotes them to phagocytose and kill foreign microorganisms [74]	Intestine	[74]
miR-375	**KLF5**: A member of the KLF family of zinc finger transcription factors which acts as a key regulator in a diverse range of important cellular functions in the body [131]. KLF5 is involved in the regulation of several processes such as cell growth, lung development, and cardiovascular apoptosis [131, 132]. It promotes proliferation and suppresses the differentiation of goblet cells [79]	HT-29 cells	[79]
miR-1968-5p	**MyD88**: A central adaptor for the TLR signaling pathway and an essential modulator of the innate immune response to microbial pathogens which initiates a cascade of signaling events leading to the expression of inflammatory-related genes. It has an important role in maintaining the mutualism between hosts and microbiota in health situations. It plays a key role in the regulation of gut injury [128]	Intestine	[128]
miR-124	**TLR6**: Toll-like receptors (TLRs) detect invading pathogens and initiate an inflammatory response that subsequently leads to induce specific adaptive immune responses [65]. TLR6, a member of the TLR family, is expressed on the surface of distinct types of immune and non-immune cells **MyD88**: Mentioned above **TNF-α**: A cytokine that is generated by various cell types, including activated macrophages, T-lymphocytes, natural killer cells, and ECs [65, 133]. It has been known as a crucial regulator of inflammatory responses and can stimulate a series of different inflammatory molecules, thus, this cytokine can be involved in the pathogenesis of several inflammatory and autoimmune diseases [133] **TRAF6**: An adaptor protein that acts as a mediator downstream of various receptor signaling with regulatory functions, including members of the TNFR superfamily, the TLR family, tumor growth factor-β receptors, and T cell receptor. Also, TRAF6 can be involved in the activation of other signaling pathways, such as NF-κB, MAPK, PI3K, and interferon regulatory factor (IRF) pathways. This molecule is necessary for the activation of the immune system as well as the maintenance of immune tolerance [134] **STAT3**: A transcription factor that is activated downstream of a wide range of cell surface receptors, including cytokine receptors [135, 136]. STAT3 signaling regulates the expression of immune factors and recruits immunosuppressive cells to create a tolerant tumor microenvironment [136]. The activated STAT3 signaling upregulates the expression of oncogenes and plays crucial roles in malignancy, cell proliferation, survival, migration, and immune evasion of many human tumors [136–138]. As such, STAT3 plays an important role in the regulation of both T and B cells. Therefore, dysfunction of STAT3 protein in lymphocytes can lead to immunodeficiency as well as autoimmune diseases [135, 136] **IL-6R**: Interleukin-6 (IL-6) activates intracellular signaling pathways via a heterodimeric signaling complex consisting of the IL-6 α-receptor (IL-6R) and the signal-transducing β-subunit glycoprotein 130 (gp130). Membrane-bound IL-6R is expressed in a limited number of cell types, including hepatocytes and lymphocytes. This mode of cell activation which IL-6 binds to its membrane-bound receptor is named classic signaling. The IL-6R can be cleaved through proteolysis which leads to the release of soluble IL-6R (sIL-6R) from the cells. The IL-6 binds to the sIL-6R which subsequently can form a signaling complex with gp130 on the cell surface. This complex activates the cells through a mode termed trans-signaling. Principally, all cells of the human body can achieve IL-6 signals by trans-signaling because of the ubiquitous expression of the gp130. Mainly, trans-signaling is causative for pro-inflammatory effects and classic signaling is responsible for anti-inflammatory properties of IL-6 [139, 140] **AHR**: A ligand-inducible transcription factor that acts as a component of the host response to environmental stimuli, is essential in the regulation of immune responses and helps to control immune homeostasis. It regulates the differentiation of Th17 and Treg cells. Activation of the intestinal AHR pathway has an anti-inflammatory effect in the gut [71]	A549 cells, BxPC3 cells, Caco-2 cells, HT-29 cells, Colon, Intestine	[65, 71, 137]
miR-19b	**SOCS3**: SOCS proteins, especially, SOCS1–3 and CISH are involved in the regulation of cytokine receptor signaling. These proteins are negative feedback regulators that are induced directly by STAT proteins and in turn act to negatively regulate the JAK/STAT pathway by various mechanisms. Due to the key roles of cytokines in the immune system, SOCS proteins can influence various aspects of immune cell behavior such as development, activation, differentiation, and polarization. They are also implicated in a range of immune-related diseases [141]. SOCS3 acts as a key regulator of immunity and inflammation via negative regulation of multiple cytokine signaling pathways such as the IL-6 family members [141, 142]	Intestine	[142]

Table 2 (continued)

miRNA	Direct target gene: Function	Epithelial cell type	References
miR-682	**PTEN**: Generally is known to repress cell survival signaling, such as Akt, and therefore promotes cell death [143]	Intestine	[143]
miR-192	**MIP-2α (CXCL2)**: A chemotactic CXC chemokine that is expressed by ECs and macrophages. It is significantly elevated in ulcerative colitis tissues [67]	Colon	[67]
miR-92b	**Sirt6**: A nicotinamide adenine dinucleotide-dependent enzyme which acts as a protective molecule. It plays roles in metabolism, aging, and disease and protects intestinal ECs against inflammatory injury [144]	Intestine	[144]
miR-346	**VDR**: A nuclear hormone receptor that mediates the biological activities of the vitamin D hormone. Epithelial VDR signaling plays a key role in maintaining the integrity of the mucosal epithelial barrier and protects against mucosal inflammation [145]	Colon, Intestine	[145]
miR-541-5p	**HMGB1**: A highly conserved nuclear protein that has a role in inflammatory progression. It is considered a putative danger signal for various inflammatory diseases. It plays a critical role in the pathogenesis of acute lung injury [146]	Alveolus	[146]
miR-145-5p	**KIF3A**: A member of the kinesin-2 family and a component of a trimeric motor complex that regulates microtubular function and transport. This complex is required for the formation and function of motile, non-motile, and sensory cilia. KIF3A plays important roles in respiratory ECs, such as barrier function, epithelial repair, and intracellular protein trafficking. Deficiency of KIF3A in respiratory ECs implicates in a high susceptibility to aeroallergens and airway hyperresponsiveness, and increases the severity of pulmonary eosinophilic inflammation and Th2-mediated inflammation following aeroallergen exposure. The human *KIF3A* gene locus is associated with susceptibility to atopic dermatitis, rhinitis, and asthma [18, 147]	Airway	[18]
miR-30c-5p	**SOCS1**: A member of the SOCS family proteins that is induced by a wide range of cytokines and known as a negative feedback inhibitor of the JAK/STAT signaling pathway induced by cytokines [148]. SOCS1 regulates various cytokines involved in the control of immunity and inflammation. For instance, it is one of the inducible negative regulators of IFN signaling [141, 148] **JAK1**: The JAK/STAT pathway is utilized by the majority of cytokine receptors to transmit signals into the nucleus for the regulation of specific genes. In mammals, the JAK family consists of 4 members (JAK1, JAK2, JAK3, and TYK2) [141]. JAK1 is widely expressed in almost all tissues and is involved in various cytokine-receptor signaling, such as IL-2R, -4R, and -6R [149]. Also, JAK1 is a key signaling component in IFN-I signaling [149, 150]	Vero E6 cells, MARC-145 cells	[148, 150]

Abbreviation: *M-CSF* Macrophage colony-stimulating factor, *KLF5* Krüppel-like factor 5, *MyD88* Myeloid differentiation primary response gene 88, *TLR6* Toll-like Receptor 6, *TNF-α* tumor necrosis factor-α, *TRAF6* TNFR-associated factor 6, *MAPK* mitogen-activated protein kinase, *PI3K* phosphoinositide 3-kinase, *STAT3* Signal transducer and activator of transcription 3, *IL-6R* Interleukin-6 receptor, *AHR* Aryl hydrocarbon receptor, *SOCS3* Suppressor of cytokine signaling 3, *CISH* cytokine-inducible SH2-containing protein, *PTEN* Phosphatase and tensin homolog, *MIP-2α* Macrophage inflammatory peptide-2α, *Sirt6* Sirtuin 6, *VDR* Vitamin D receptor, *HMGB1* High-mobility group box 1, *KIF3A* Kinesin family member 3A, *SOCS1* Suppressor of cytokine signaling protein 1, *JAK1* Janus kinase 1

Cells: *HT-29* human colon adenocarcinoma cell line, *A549* human pulmonary epithelial cell line, *BxPC3* human pancreatic cell line, *Caco-2* human colon cancer cell line, *Vero E6* kidney epithelial cells isolated from an African green monkey, *MARC-145* monkey kidney epithelial cell line

which among them plant miRNAs are the main source of these exogenous RNAs. Upon dietary intake, xeno-miRs from different sources such as plant [161–164] and milk [165, 166] are absorbed by gastrointestinal ECs, packaged into exosomes, subsequently secreted into the blood circulation and then delivered into recipient tissues/ cells [161, 163, 164], including the lung, liver, spleen, kidney, heart, DCs, adipocytes and macrophages [161, 163, 164, 167–171], where they regulate host- gene expression [163, 167, 172].

Numerous studies have confirmed the immunomodulatory effects of xeno-miRs on the mammalian immune system. Cavalieri et al. demonstrated that a wide range of miRNAs obtained from diverse plant species could act as TLR3 ligands in DCs. Also, they found that plant xenomiRs (for instance, Fragaria vesca miR168), via impairment of TRIF signaling, were able to reduce inflammation and the pathology development of autoimmune encephalomyelitis in the mouse model [168].

Plant miR159a and miR156c in nut exosome-like nanovesicles were found to have anti-inflammatory effects in vitro and in mouse models of adipose tissue inflammation via downregulation of TNF receptor superfamily member 1a (Tnfrsf1a) expression in macrophages and adipocytes, which in turn negatively regulate TNF-α signaling pathway [167]. Zhou et al. study suggested that absorbed plant miR2911 from honeysuckle decoction was transferred into the lung by exosomes through circulation, where it inhibited SARS-CoV-2 replication and accelerated the recovery process in COVID-19 patients [171].

Another study reported that plant miR2911, encoded by honeysuckle, directly targeted various influenza A viruses and inhibited viral replication [164]. Ginger

Table 3 MiRNAs expressed in epithelial cells (ECs) and their respective function in the immune system and immune disorders

miRNA	Physiological or pathological conditions	Expression of miR	Function	References
miR-128	*Salmonella enterica* infection	Upregulation in HT29 cells, mouse intestine, and colon tissues	- Decrease the secretion of M-CSF by host ECs and the M-CSF–mediated macrophage recruitment, a mechanism by which *Salmonella* escapes macrophages	[74]
miR-375	Nude mice that suffer an ineffective Th2 response	Less expression in the colon of nude mice	✓ IL-13 or activated PI[3]K pathway induced more miR-375 expression in HT-29 cells and nude mice ✓ More miR-375 expression was involved in: - Induction of RELMβ which in turn enhances an antiparasitic immune response - Induction of TSLP that promotes mucosal Th2 activation while suppressing the Th1 arm - Goblet cell differentiation and function by suppressing KLF5 protein	[79]
miR-1968-5p	Radiation-induced intestinal injury in mice	Upregulation in the mouse small intestine after hydrogen-water oral administration	- Downregulation of MyD88 expression in small intestine tissues and retention of intestinal bacterial composition in irradiated mice - Alleviation of intestinal injury induced by irradiation in mice	[128]
miR-124	*Mycobacterium bovis* Bacillus Calmette-Guerin (BCG) infection	Upregulation in A549 cells and murine lung	- Direct regulation and repression of multiple components in the TLR signaling, including TLR6, MyD88, TRAF6, and TNF-α in response to BCG infection - Attenuation of the BCG-induced inflammatory response by down-regulating the production of pro-inflammatory cytokines, including NF-κB, IFN-β, IL-1α, IL-8 -Down-regulation of MyD88 via negative feedback mechanism to hinder a severe inflammatory response during mycobacterial infection	[65]
miR-124	Pancreatic ductal adenocarcinoma	Down-regulation in BxPC3 cells compared to normal pancreatic cell line	✓ Effects of transient overexpression of miR-124 on BxPC3 cells were as below: - Inhibition of cell proliferation through reducing the expression of IL-6R and STAT3 - Repression of colony formation - Reduction of cell viability	[137]
Pre-mir-124	Crohn's disease (CD)	Up-regulation in active CD tissues and intestinal ECs	- Up-regulation of the expression of pro-inflammatory cytokines (TNF-α, IL-1β, and IL-6) by reducing AHR protein level, which promotes the pathogenesis of CD	[71]

Table 3 (continued)

miRNA	Physiological or pathological conditions	Expression of miR	Function	References
miR-19b	Crohn's disease (CD)	Down-regulation in CD patient intestinal tissues	✓ Effects of overexpression of pre-mir-19b on Caco2 cells and administration of that in a mouse model were as below: - Modulation of chemokine (such as MIP-3α) production and reduction of intestinal inflammation via down-regulating SOCS3 protein -Decrease the severity of CD	[142]
miR-682	Intestinal ischemia–reperfusion (I/R) injury	Up-regulation in intestinal ECs during ischemia in mice and in the human colonic ECs during hypoxia, but was undetected rapidly after intestinal reperfusion in intestinal EC of mice	✓ Lentivirus-mediated miR-682 overexpression in vivo during intestinal reperfusion or miR-682 mimic transfection in vitro during hypoxia led to: - Decrease the expression of PTEN and subsequently activation of NF-κB p65 - Suppression of hypoxia-induced cell apoptosis via PTEN/NF-κB p65 pathway - Repression of mitochondrial-mediated apoptosis in intestinal EC of mice - Protection against intestinal I/R injury through PTEN/NF-κB p65 pathway	[143]
miR-192	Active ulcerative colitis (UC)	Down-regulation in colonic EC	- miR-192 may play a key role in processes of inflammation and fibrosis, however, the exact role of that was not fully investigated in this study	[67]
miR-346	Inflammatory bowel diseases (IBD)	Up-regulation in human IBD biopsies and colitis mouse model	- Mediates the suppressive effect of TNF-α on the expression of gut epithelial VDR, which in turn compromises the integrity of the mucosal epithelial barrier, further drives mucosal inflammation, and contributes to the development of IBD	[145]
miR-541-5p	Acute lung injury (ALI)	Down-regulation in ALI tissues and the LPS-induced type II alveolar epithelial (ATII) cell model	✓ Overexpression of miR-541-5p in the LPS-induced ATII cell model: - Promotes cell activity and proliferation and suppresses the inflammatory response through modulation of the HMGB1/JNK/ERK/p38 pathway	[146]
miR-145-5p	Asthma	Upregulation in airway ECs of house dust mite (HDM)-exposed asthmatic mice	- Promotes the HDM-induced release of inflammatory chemokines by the airway epithelium and epithelial barrier dysfunction - Inhibits epithelial repair via directly targeting KIF3A - Exacerbates the HDM-induced Th2 immune response	[18]
miR-30c-5p	Porcine epidemic diarrhea virus (PEDV) infection	Down-regulation in Vero E6 cells	✓ Down-regulation of miR-30c-5p, and thus increasing SOCS1 expression at the late stage of infection: -Plays a role in PEDV escape from the response of IFN-λ through the miR-30a-5p/SOCS1 axis	[148]

Table 3 (continued)

miRNA	Physiological or pathological conditions	Expression of miR	Function	References
miR-136	Influenza A virus infection	Up-regulation in A549 cells	- Suppresses the activity of H5N1 influenza A virus, as well as vesicular stomatitis virus in A549 cells - Regulates host antiviral innate immunity by acting as a ligand for RIG-I, thereby causing IL-6 and IFN-β accumulation in A549 cells	[70]
miR-17-3p and miR-221	Influenza A virus infection	Downregulation in human alveolar basal ECs during the early stage of infection	- Downregulation of these two miRNAs enhances viral replication possibly through GALNT3 upregulation	[154]
miR-155	*Pseudomonas aeruginosa* infection	Up-regulation in human and mouse corneas	- Suppresses the macrophage-mediated elimination of *P. aeruginosa* by targeting Rheb, and promotes corneal susceptibility to *P. aeruginosa* keratitis	[155]

Abbreviation: *M-CSF* Macrophage colony-stimulating factor, *MyD88* Myeloid differentiation primary response gene 88, *RELMβ* Resistin-like molecule β, *TSLP* Thymic stromal lymphopoietin, *KLF5* Krüppel-like factor 5, *TRAF6* TNFR-associated factor 6, *STAT3* Signal transducer and activator of transcription 3, *AHR* Aryl hydrocarbon receptor, *MIP-3α* Macrophage inflammatory peptide, *SOCS3* Suppressor of cytokine signaling 3, *PTEN* Phosphatase and tensin homolog, *VDR* Vitamin D receptor, *KIF3A* Kinesin family member 3A, *SOCS1* Suppressor of cytokine signaling protein 1, *RIG-I* Retinoic acid-inducible gene 1, *GALNT3* GalNAc transferase 3, *Rheb* Ras homolog enriched in brain exosome-like nanoparticle miRNAs (aly-miR396a-5p and rlcv-miR rL1-28-3p) reduced SARS-CoV-2-induced lung inflammation and apoptosis via inhibition of expression of viral RNA polymerase Nsp12 and spike genes [170].

Moreover, diet-derived exosome-like nanoparticles containing miRNAs can be taken up by the gut microbiota and are able to modulate their composition and function in mammals. In this regard, Teng et al. reported that mdo-miR7267-3p, one of the miRNAs present in ginger exosome-like nanoparticles, repressed monooxygenase ycnE expression in *Lactobacillus rhamnosus*, which increased the production of indole-3-carboxaldehyde (I3A)—— a ligand for aryl hydrocarbon receptor (AHR)—— leading to the induction of IL-22 production via activation of AHR pathway in gut lymphocytes. These actions improved gut barrier function and ameliorated colitis in mice [173]. Another study reported that bovine milk-derived extracellular vesicles through immune-related miRNAs changed gut microbiota composition, modulated their metabolites, and strengthened intestinal immunity in mice [174].

Interestingly, Li et al. study provided evidence that plant miRNAs (for instance, miR2911 derived from honeysuckle) in the maternal diet can be delivered to the fetus through the placenta and regulate fetal gene expression [162].

However, the direct effects of xeno-miRs on the immunomodulatory functions of ECs as well as xeno-miR-mediated cross-talk between ECs and neighboring immune cells have not been deeply explored yet. Future research in this field opens promising avenues for miRNA-based treatment of immune malignancies through diet.

It is noteworthy to underline that despite the above-mentioned evidence, several researchers have reported negative/negligible expression of xeno-miRs in body fluids or tissues of recipients and rejected the xeno-miR hypothesis [175–177]. It seems that technical issues such as experimental artifacts and cross-contaminations [176], xeno-miR degradation during the digestive process [175], and being selective of diet-derived xenomiR absorption (dependent on miR sequence) by animals [178] are the possible causes for studies where xeno-miRs were not detected in animal bodies. However, further studies are needed to resolve these contradictions.

Therapeutic potential of miRNAs to treat conditions involving EC disorders

In the context of miRNA roles in immunoregulatory functions of ECs, promising therapeutic applications of miRNAs are to use their immunomodulatory capacities to induce antimicrobial pathways during infection as well as to control the deregulated inflammatory responses in immune-related disorders such as IBD and asthma (as noted in Table 3). For instance, miR-128 level in mouse intestinal and colon tissues was upregulated during *Salmonella enterica* infection. The elevation in miR-128 level decreased the secretion of M-CSF by host ECs and the M-CSF–mediated macrophage recruitment, leading to the escape of *Salmonella* from macrophages (Fig. 1). On the other hand, intragastric delivery of anti-miR-128 promoted M-CSF–induced macrophage recruitment and suppressed *S. enterica* infection in mice [74]. However, despite extensive studies confirming potential therapeutic applications of miRNAs, few studies have been conducted as clinical trials and none of those have reached phase III [179] or led to Food and Drug Administration (FDA)– approved drug. Thus, it seems that the translation of these research findings into clinical treatments faces significant challenges.

As an example of miRNA-based therapy targeting ECs, we refer to the RG-101 designed for use in patients with chronic hepatitis C virus (HCV) infection. In which anti-miR-122 oligonucleotide was conjugated to N-acetylgalactosamine– a high-affinity ligand for the asialoglycoprotein receptor that is widely expressed on hepatocytes [180]. It is interesting to note that miR-122 was known as a crucial host factor for HCV replication. It binds to 5´ UTR of the HCV RNA and enhances genome stability and translation [181]. To evaluate the safety and efficacy of RG-101 in human subjects, 32 patients were enrolled in phase 1B randomized controlled trial study. The results showed that a single subcutaneous injection of RG-101 significantly reduced viral load in patients at week 4 of treatment. In addition, HCV RNA levels substantially decreased in all treated patients and were not detectable for at least 76 weeks (end of follow-up) in 3 patients with sustained virological response. Nonetheless, viral rebound– which is associated with mutations in miR-122 binding regions in the HCV 5´ UTR– was observed in most patients. Some severe adverse events, including intrahepatic cholestasis and hyperbilirubinemia, were reported in some patients [180]. Antiviral immunity analysis showed that NK-cell frequency increased and NK-cell activating receptors (such as NKp30 and NKp46), NK-cell IFN-γ production, and IFN-γ-induced protein 10 (IP-10) level in plasma decreased after RG-101 administration. Moreover, HCV-specific T-cell responses did not significantly change in patients. Overall, the data suggested that the NK cells, and not adaptive immunity, may have involved in the control of HCV infection [182]. Given that miR-122 acts as a tumor suppressor in hepatocellular carcinoma [183], the possibility of long-term risk of hepatocellular carcinoma development in patients with HCV infection following RG-101 administration should be noticed.

In another phase 1 clinical trial study, the safety, optimal dosing, and efficacy of TargomiRs were tested in patients with malignant pleural mesothelioma (MPM). TargomiRs were developed as minicells loaded with miR-16 mimic with an anti-EGFR bispecific antibody to target EGFR-expressing tumor cells [184]. Mesothelial cells have characteristics of both mesenchymal and epithelial cells which line the serosal cavities (peritoneal, pericardial, and pleural) and internal organs [185, 186]. MiR-16 was reported to have tumor suppressor activity in MPM [187].

In the above-mentioned study, 26 patients received at least one dose of TargomiR. During the response evaluation, the following results were observed in patients: 5% with a partial response, 68% with stable disease, and 27% with progressive disease. Moreover, toxicity effects, such as inflammation symptoms, anaphylaxis, and cardiac events, which were dependent on the dose of TargomiR administration, were recorded [184].

In sum, although it is now clarified that miRNAs are key regulators of gene expression and their dysfunction is involved in many diseases, attempts to produce miRNA-based therapies did not end with a practical outcome. This issue is partly related to the inherent characteristics of miRNAs, including a large number of endogenous targets, low binding affinity with its target which leads to nonspecific actions, and degradation of miRNA mimics/ anti-miRNAs by circulating RNase enzymes [179]. In addition, severe immune-mediated adverse reactions, such as those were observed in MRX34 administration in several patients with advanced solid tumors [188], are other obstacles that remain to be overcome. Nevertheless, the development of the targeted delivery system in which miR mimics/anti-miRs were transported to the specific tissue, can improve the efficacy and safety of a miR-based therapy [179].

In total, considering the above-mentioned points, we believe that a safe therapeutic compound that restores disordered host cells to compensate deregulated miRNA at its physiological level rather than exogenously transferred miRNA mimics /anti-miRNAs could be beneficial to resolve the challenges related to the miR-based therapeutics. Further research is needed to be directed to identifying these compounds and their molecular mechanisms of action.

Conclusion

Taken together, the studies summarized in this review illustrate the various and multifaceted roles of miRNAs in the immunoregulatory functions of ECs. Although we attempted to provide a comprehensive review, however, an in-depth overview of all aspects related to this issue was not possible in the current paper due to space limitations. For example, with regard to this issue, one of the valuable aspects can be a deep understanding of the role of miRNAs in cross-talk between microbiota, ECs, and the immune system. However, it is very beneficial and practical that reliable knowledge provided from a comprehensive review be translated into the development of novel therapeutics supporting human health.

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References

1. Larsen SB, Cowley CJ, Fuchs E. Epithelial cells: liaisons of immunity. Curr Opin Immunol. 2020;62:45–53.
2. Hewitt RJ, Lloyd CM. Regulation of immune responses by the airway epithelial cell landscape. Nat Rev Immunol. 2021;21(6):347–62.
3. Sharma L, Feng J, Britto CJ, Dela Cruz CS. Mechanisms of epithelial immunity evasion by respiratory bacterial pathogens. Front Immunol. 2020;11:91.
4. Jafari N, Abediankenari S. MicroRNA-34 dysregulation in gastric cancer and gastric cancer stem cell. Tumour Biol. 2017;39(5):1010428317701652.
5. O'Brien J, Hayder H, Zayed Y, Peng C. Overview of MicroRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne). 2018;9:402.
6. Jafari N, Abediankenari S, Hossein-Nataj H. miR-34a mimic or pre-mir-34a, which is the better option for cancer therapy? KatoIII as a model to study miRNA action in human gastric cancer cells. Cancer Cell Int. 2021;21(1):178.
7. An J, Chen X, Chen W, Liang R, Reinach PS, Yan D, et al. MicroRNA expression profile and the role of miR-204 in corneal wound healing. Invest Ophthalmol Vis Sci. 2015;56(6):3673–83.
8. Li D, Li XI, Wang A, Meisgen F, Pivarcsi A, Sonkoly E, et al. MicroRNA-31 promotes skin wound healing by enhancing keratinocyte proliferation and migration. J Invest Dermatol. 2015;135(6):1676–85.
9. Tang H, Wang X, Zhang M, Yan Y, Huang S, Ji J, et al. MicroRNA-200b/c-3p regulate epithelial plasticity and inhibit cutaneous wound healing by modulating TGF-beta-mediated RAC1 signaling. Cell Death Dis. 2020;11(10):931.

10. Cichon C, Sabharwal H, Ruter C, Schmidt MA. MicroRNAs regulate tight junction proteins and modulate epithelial/endothelial barrier functions. Tissue Barriers. 2014;2(4):e944446.
11. Soroosh A, Rankin CR, Polytarchou C, Lokhandwala ZA, Patel A, Chang L, et al. miR-24 Is elevated in ulcerative colitis patients and regulates intestinal epithelial barrier function. Am J Pathol. 2019;189(9):1763–74.
12. Li ZN, Ge MX, Yuan ZF. MicroRNA-182-5p protects human lens epithelial cells against oxidative stress-induced apoptosis by inhibiting NOX4 and p38 MAPK signalling. BMC Ophthalmol. 2020;20(1):233.
13. Wang S, Yu M, Yan H, Liu J, Guo C. MiR-34a-5p negatively regulates oxidative stress on lens epithelial cells by silencing GPX3 - a novel target. Curr Eye Res. 2022;47(5):727–34.
14. Akkoc Y, Gozuacik D. MicroRNAs as major regulators of the autophagy pathway. Biochim Biophys Acta Mol Cell Res. 2020;1867(5): 118662.
15. Kawasaki H, Amano H. Anti-inflammatory role of microRNA-429 in human gingival epithelial cells-inhibition of IL-8 production through direct binding to IKKbeta mRNA. Mol Med Rep. 2021;24(2).
16. Nakato G, Hase K, Sato T, Kimura S, Sakakibara S, Sugiyama M, et al. Epithelium-Intrinsic MicroRNAs contribute to mucosal immune homeostasis by promoting M-cell maturation. PLoS ONE. 2016;11(3):e0150379.
17. Deng M, Hu J, Tong R, Guo H, Li X, Liu Y. miR-452-5p regulates the responsiveness of intestinal epithelial cells in inflammatory bowel disease through Mcl-1. Exp Ther Med. 2021;22(2):813.
18. Xiong T, Du Y, Fu Z, Geng G. MicroRNA-145-5p promotes asthma pathogenesis by inhibiting kinesin family member 3A expression in mouse airway epithelial cells. J Int Med Res. 2019;47(7):3307–19.
19. Peterson LW, Artis D. Intestinal epithelial cells: regulators of barrier function and immune homeostasis. Nat Rev Immunol. 2014;14(3):141–53.
20. Mvubu NE, Pillay B, McKinnon LR, Pillay M. Mycobacterium tuberculosis strains induce strain-specific cytokine and chemokine response in pulmonary epithelial cells. Cytokine. 2018;104:53–64.
21. Chiba H, Osanai M, Murata M, Kojima T, Sawada N. Transmembrane proteins of tight junctions. Biochim Biophys Acta. 2008;1778(3):588–600.
22. Tsukita S, Katsuno T, Yamazaki Y, Umeda K, Tamura A, Tsukita S. Roles of ZO-1 and ZO-2 in establishment of the belt-like adherens and tight junctions with paracellular permselective barrier function. Ann N Y Acad Sci. 2009;1165:44–52.
23. Huang Y, Liu HM, Mao QY, Cong X, Zhang Y, Lee SW, et al. High glucose reduces the paracellular permeability of the submandibular gland epithelium via the MiR-22–3p/Sp1/Claudin pathway. Cells. 2021;10(11).
24. Yuki T, Tobiishi M, Kusaka-Kikushima A, Ota Y, Tokura Y. Impaired tight junctions in atopic dermatitis skin and in a skin-equivalent model treated with interleukin-17. PLoS ONE. 2016;11(9): e0161759.
25. Krug SM, Bojarski C, Fromm A, Lee IM, Dames P, Richter JF, et al. Tricellulin is regulated via interleukin-13-receptor alpha2, affects macromolecule uptake, and is decreased in ulcerative colitis. Mucosal Immunol. 2018;11(2):345–56.
26. Minns D, Smith KJ, Alessandrini V, Hardisty G, Melrose L, Jackson-Jones L, et al. The neutrophil antimicrobial peptide cathelicidin promotes Th17 differentiation. Nat Commun. 2021;12(1):1285.
27. Geitani R, Moubareck CA, Costes F, Marti L, Dupuis G, Sarkis DK, et al. Bactericidal effects and stability of LL-37 and CAMA in the presence of human lung epithelial cells. Microbes Infect. 2022;24(3):104928.
28. Di Nardo A, Yamasaki K, Dorschner RA, Lai Y, Gallo RL. Mast cell cathelicidin antimicrobial peptide prevents invasive group A Streptococcus infection of the skin. J Immunol. 2008;180(11):7565–73.
29. Castaneda-Sanchez JI, Dominguez-Martinez DA, Olivar-Espinosa N, Garcia-Perez BE, Lorono-Pino MA, Luna-Herrera J, et al. Expression of antimicrobial peptides in human monocytic cells and neutrophils in response to dengue virus type 2. Intervirology. 2016;59(1):8–19.
30. Xu B, Wu X, Gong Y, Cao J. IL-27 induces LL-37/CRAMP expression from intestinal epithelial cells: implications for immunotherapy of Clostridioides difficile infection. Gut Microbes. 2021;13(1):1968258.
31. Hase K, Murakami M, Iimura M, Cole SP, Horibe Y, Ohtake T, et al. Expression of LL-37 by human gastric epithelial cells as a potential host defense mechanism against Helicobacter pylori. Gastroenterology. 2003;125(6):1613–25.
32. Bucki R, Byfield FJ, Janmey PA. Release of the antimicrobial peptide LL-37 from DNA/F-actin bundles in cystic fibrosis sputum. Eur Respir J. 2007;29(4):624–32.
33. Yim S, Dhawan P, Ragunath C, Christakos S, Diamond G. Induction of cathelicidin in normal and CF bronchial epithelial cells by 1,25-dihydroxyvitamin D(3). J Cyst Fibros. 2007;6(6):403–10.
34. Ho J, Wickramasinghe DN, Nikou SA, Hube B, Richardson JP, Naglik JR. Candidalysin is a potent trigger of alarmin and antimicrobial peptide release in epithelial cells. Cells. 2020;9(3).
35. Byfield FJ, Kowalski M, Cruz K, Leszczynska K, Namiot A, Savage PB, et al. Cathelicidin LL-37 increases lung epithelial cell stiffness, decreases transepithelial permeability, and prevents epithelial invasion by Pseudomonas aeruginosa. J Immunol. 2011;187(12):6402–9.
36. Kang J, Dietz MJ, Li B. Antimicrobial peptide LL-37 is bactericidal against Staphylococcus aureus biofilms. PLoS ONE. 2019;14(6):e0216676.
37. Noore J, Noore A, Li B. Cationic antimicrobial peptide LL-37 is effective against both extra- and intracellular Staphylococcus aureus. Antimicrob Agents Chemother. 2013;57(3):1283–90.
38. Currie SM, Findlay EG, McHugh BJ, Mackellar A, Man T, Macmillan D, et al. The human cathelicidin LL-37 has antiviral activity against respiratory syncytial virus. PLoS ONE. 2013;8(8): e73659.
39. Xhindoli D, Pacor S, Benincasa M, Scocchi M, Gennaro R, Tossi A. The human cathelicidin LL-37–A pore-forming antibacterial peptide and host-cell modulator. Biochim Biophys Acta. 2016;1858(3):546–66.
40. Wan M, van der Does AM, Tang X, Lindbom L, Agerberth B, Haeggstrom JZ. Antimicrobial peptide LL-37 promotes bacterial phagocytosis by human macrophages. J Leukoc Biol. 2014;95(6):971–81.
41. Neumann A, Berends ET, Nerlich A, Molhoek EM, Gallo RL, Meerloo T, et al. The antimicrobial peptide LL-37 facilitates the formation of neutrophil extracellular traps. Biochem J. 2014;464(1):3–11.
42. Jiao D, Wong CK, Tsang MS, Chu IM, Liu D, Zhu J, et al. Activation of Eosinophils Interacting with Bronchial Epithelial Cells by Antimicrobial Peptide LL-37: Implications in Allergic Asthma. Sci Rep. 2017;7(1):1848.
43. Mahlapuu M, Hakansson J, Ringstad L, Bjorn C. Antimicrobial Peptides: An Emerging Category of Therapeutic Agents. Front Cell Infect Microbiol. 2016;6:194.
44. Bemark M, Angeletti D. Know your enemy or find your friend?-Induction of IgA at mucosal surfaces. Immunol Rev. 2021;303(1):83–102.
45. Lycke NY, Bemark M. The regulation of gut mucosal IgA B-cell responses: recent developments. Mucosal Immunol. 2017;10(6):1361–74.
46. Sobia P, Pillay T, Liebenberg LJP, Sivro A, Mansoor LE, Osman F, et al. Higher mucosal antibody concentrations in women with genital tract inflammation. Sci Rep. 2021;11(1):23514.
47. Roux ME, McWilliams M, Phillips-Quagliata JM, Weisz-Carrington P, Lamm ME. Origin of IgA-secreting plasma cells in the mammary gland. J Exp Med. 1977;146(5):1311–22.
48. Wilmore JR, Gaudette BT, Gomez Atria D, Rosenthal RL, Reiser SK, Meng W, et al. IgA Plasma Cells Are Long-Lived Residents of Gut and Bone Marrow That Express Isotype- and Tissue-Specific Gene Expression Patterns. Front Immunol. 2021;12:791095.
49. Rojas OL, Probstel AK, Porfilio EA, Wang AA, Charabati M, Sun T, et al. Recirculating intestinal IgA-producing cells regulate neuroinflammation via IL-10. Cell. 2019;176(3):610–24 e18.
50. Tezuka H, Ohteki T. Regulation of IgA production by intestinal dendritic cells and related cells. Front Immunol. 2019;10:1891.
51. Li Y, Jin L, Chen T. The Effects of Secretory IgA in the Mucosal Immune System. Biomed Res Int. 2020;2020:2032057.
52. Cerutti A. The regulation of IgA class switching. Nat Rev Immunol. 2008;8(6):421–34.
53. Nguyen AV, Soulika AM. The dynamics of the skin's immune system. Int J Mol Sci. 2019;20(8).
54. Skibba ME, Xu X, Weiss K, Huisken J, Brasier AR. Role of Secretoglobin(+) (club cell) NFkappaB/RelA-TGFbeta signaling in aero-allergen-induced epithelial plasticity and subepithelial myofibroblast transdifferentiation. Respir Res. 2021;22(1):315.
55. Zeuthen LH, Fink LN, Frokiaer H. Epithelial cells prime the immune response to an array of gut-derived commensals towards a tolerogenic phenotype through distinct actions of thymic stromal lymphopoietin and transforming growth factor-beta. Immunology. 2008;123(2):197–208.
56. Zaph C, Troy AE, Taylor BC, Berman-Booty LD, Guild KJ, Du Y, et al. Epithelial-cell-intrinsic IKK-beta expression regulates intestinal immune homeostasis. Nature. 2007;446(7135):552–6.

57. Kouzaki H, Tojima I, Kita H, Shimizu T. Transcription of interleukin-25 and extracellular release of the protein is regulated by allergen proteases in airway epithelial cells. Am J Respir Cell Mol Biol. 2013;49(5):741–50.
58. Deng C, Peng N, Tang Y, Yu N, Wang C, Cai X, et al. Roles of IL-25 in Type 2 Inflammation and Autoimmune Pathogenesis. Front Immunol. 2021;12: 691559.
59. Tang SC, Liao PY, Hung SJ, Ge JS, Chen SM, Lai JC, et al. Topical application of glycolic acid suppresses the UVB induced IL-6, IL-8, MCP-1 and COX-2 inflammation by modulating NF-kappaB signaling pathway in keratinocytes and mice skin. J Dermatol Sci. 2017;86(3):238–48.
60. Chen SC, Constantinides C, Kebschull M, Papapanou PN. MicroRNAs regulate cytokine responses in gingival epithelial cells. Infect Immun. 2016;84(12):3282–9.
61. Meisgen F, Xu Landen N, Wang A, Rethi B, Bouez C, Zuccolo M, et al. MiR-146a negatively regulates TLR2-induced inflammatory responses in keratinocytes. J Invest Dermatol. 2014;134(7):1931–40.
62. Peng XD, Zhao GQ, Lin J, Jiang N, Xu Q, Zhu CC, et al. Fungus induces the release of IL-8 in human corneal epithelial cells, via Dectin-1-mediated protein kinase C pathways. Int J Ophthalmol. 2015;8(3):441–7.
63. Eckmann L, Kagnoff MF, Fierer J. Epithelial cells secrete the chemokine interleukin-8 in response to bacterial entry. Infect Immun. 1993;61(11):4569–74.
64. Claud EC, Savidge T, Walker WA. Modulation of human intestinal epithelial cell IL-8 secretion by human milk factors. Pediatr Res. 2003;53(3):419–25.
65. Ma C, Li Y, Zeng J, Wu X, Liu X, Wang Y. Mycobacterium bovis BCG triggered MyD88 induces miR-124 feedback negatively regulates immune response in alveolar epithelial cells. PLoS ONE. 2014;9(4): e92419.
66. Brenaut P, Lefevre L, Rau A, Laloe D, Pisoni G, Moroni P, et al. Contribution of mammary epithelial cells to the immune response during early stages of a bacterial infection to Staphylococcus aureus. Vet Res. 2014;45(1):16.
67. Wu F, Zikusoka M, Trindade A, Dassopoulos T, Harris ML, Bayless TM, et al. MicroRNAs are differentially expressed in ulcerative colitis and alter expression of macrophage inflammatory peptide-2 alpha. Gastroenterology. 2008;135(5):1624–3524.
68. Scheller J, Chalaris A, Schmidt-Arras D, Rose-John S. The pro- and anti-inflammatory properties of the cytokine interleukin-6. Biochim Biophys Acta. 2011;1813(5):878–88.
69. Li C, Zhao G, Che C, Lin J, Li N, Hu L, et al. The Role of LOX-1 in Innate Immunity to Aspergillus fumigatus in Corneal Epithelial Cells. Invest Ophthalmol Vis Sci. 2015;56(6):3593–603.
70. Zhao L, Zhu J, Zhou H, Zhao Z, Zou Z, Liu X, et al. Identification of cellular microRNA-136 as a dual regulator of RIG-I-mediated innate immunity that antagonizes H5N1 IAV replication in A549 cells. Sci Rep. 2015;5:14991.
71. Zhao Y, Ma T, Chen W, Chen Y, Li M, Ren L, et al. MicroRNA-124 Promotes Intestinal Inflammation by Targeting Aryl Hydrocarbon Receptor in Crohn's Disease. J Crohns Colitis. 2016;10(6):703–12.
72. Buerger C, Richter B, Woth K, Salgo R, Malisiewicz B, Diehl S, et al. Interleukin-1beta interferes with epidermal homeostasis through induction of insulin resistance: implications for psoriasis pathogenesis. J Invest Dermatol. 2012;132(9):2206–14.
73. Zhao J, Wu XY, Yu FSX. Activation of Toll-like receptors 2 and 4 in Aspergillus fumigatus keratitis. Innate Immun. 2009;15(3):155–68.
74. Zhang T, Yu J, Zhang Y, Li L, Chen Y, Li D, et al. Salmonella enterica serovar enteritidis modulates intestinal epithelial miR-128 levels to decrease macrophage recruitment via macrophage colony-stimulating factor. J Infect Dis. 2014;209(12):2000–11.
75. Dumbuya J, Prentice H, Wu JY. Role of Granulocyte-Colony Stimulating Factor (G-CSF) in Immune Regulation and Neuroprotection. J Cell Immunol. 2023;5(1):7–9.
76. Franzke A. The role of G-CSF in adaptive immunity. Cytokine Growth Factor Rev. 2006;17(4):235–44.
77. Egea L, Hirata Y, Kagnoff MF. GM-CSF: a role in immune and inflammatory reactions in the intestine. Expert Rev Gastroenterol Hepatol. 2010;4(6):723–31.
78. Bhattacharya P, Thiruppathi M, Elshabrawy HA, Alharshawi K, Kumar P, Prabhakar BS. GM-CSF: An immune modulatory cytokine that can suppress autoimmunity. Cytokine. 2015;75(2):261–71.
79. Biton M, Levin A, Slyper M, Alkalay I, Horwitz E, Mor H, et al. Epithelial microRNAs regulate gut mucosal immunity via epithelium-T cell crosstalk. Nat Immunol. 2011;12(3):239–46.
80. Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsiak D, Wang X, et al. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. J Exp Med. 2013;210(13):2939–50.
81. Matti C, D'Uonnolo G, Artinger M, Melgrati S, Salnikov A, Thelen S, et al. CCL20 is a novel ligand for the scavenging atypical chemokine receptor 4. J Leukoc Biol. 2020;107(6):1137–54.
82. Xu M, Lu H, Lee YH, Wu Y, Liu K, Shi Y, et al. An interleukin-25-mediated autoregulatory circuit in keratinocytes plays a pivotal role in psoriatic skin inflammation. Immunity. 2018;48(4):787–98 e4.
83. Gerbe F, Sidot E, Smyth DJ, Ohmoto M, Matsumoto I, Dardalhon V, et al. Intestinal epithelial tuft cells initiate type 2 mucosal immunity to helminth parasites. Nature. 2016;529(7585):226–30.
84. Angkasekwinai P, Park H, Wang YH, Wang YH, Chang SH, Corry DB, et al. Interleukin 25 promotes the initiation of proallergic type 2 responses. J Exp Med. 2007;204(7):1509–17.
85. Pietka W, Khnykin D, Bertelsen V, Lossius AH, Stav-Noraas TE, Hol Fosse J, et al. Hypo-osmotic Stress Drives IL-33 Production in Human Keratinocytes-An Epidermal Homeostatic Response. J Invest Dermatol. 2019;139(1):81–90.
86. Zhang W, Du JY, Yu Q, Jin JO. Interleukin-7 produced by intestinal epithelial cells in response to Citrobacter rodentium infection plays a major role in innate immunity against this pathogen. Infect Immun. 2015;83(8):3213–23.
87. Shalapour S, Deiser K, Kuhl AA, Glauben R, Krug SM, Fischer A, et al. Interleukin-7 links T lymphocyte and intestinal epithelial cell homeostasis. PLoS ONE. 2012;7(2): e31939.
88. Notas G, Alexaki VI, Kampa M, Pelekanou V, Charalampopoulos I, Sabour-Alaoui S, et al. APRIL binding to BCMA activates a JNK2-FOXO3-GADD45 pathway and induces a G2/M cell growth arrest in liver cells. J Immunol. 2012;189(10):4748–58.
89. Pelekanou V, Notas G, Theodoropoulou K, Kampa M, Takos D, Alexaki VI, et al. Detection of the TNFSF members BAFF, APRIL, TWEAK and their receptors in normal kidney and renal cell carcinomas. Anal Cell Pathol (Amst). 2011;34(1–2):49–60.
90. He B, Xu W, Santini PA, Polydorides AD, Chiu A, Estrella J, et al. Intestinal bacteria trigger T cell-independent immunoglobulin A(2) class switching by inducing epithelial-cell secretion of the cytokine APRIL. Immunity. 2007;26(6):812–26.
91. Vincent FB, Saulep-Easton D, Figgett WA, Fairfax KA, Mackay F. The BAFF/APRIL system: emerging functions beyond B cell biology and autoimmunity. Cytokine Growth Factor Rev. 2013;24(3):203–15.
92. Alexaki VI, Pelekanou V, Notas G, Venihaki M, Kampa M, Dessirier V, et al. B-cell maturation antigen (BCMA) activation exerts specific proinflammatory effects in normal human keratinocytes and is preferentially expressed in inflammatory skin pathologies. Endocrinology. 2012;153(2):739–49.
93. Korbecki J, Bosiacki M, Barczak K, Lagocka R, Brodowska A, Chlubek D, et al. Involvement in Tumorigenesis and Clinical Significance of CXCL1 in Reproductive Cancers: Breast Cancer, Cervical Cancer, Endometrial Cancer, Ovarian Cancer and Prostate Cancer. Int J Mol Sci. 2023;24(8).
94. Arunachalam D, Namperumalsamy VP, Prajna L, Kuppamuthu D. Human Corneal epithelial cells internalize aspergillus flavus spores by actin-mediated endocytosis. Infect Immun. 2021;89(6).
95. Arunachalam D, Ramanathan SM, Menon A, Madhav L, Ramaswamy G, Namperumalsamy VP, et al. Expression of immune response genes in human corneal epithelial cells interacting with Aspergillus flavus conidia. BMC Genomics. 2022;23(1):5.
96. Li C, Zhao GQ, Che CY, Li N, Lin J, Xu Q, et al. Expression of dectin-1 during fungus infection in human corneal epithelial cells. Int J Ophthalmol. 2014;7(1):34–7.
97. Jie Z, Wu XY, Yu FS. Activation of Toll-like receptors 2 and 4 in Aspergillus fumigatus keratitis. Innate Immun. 2009;15(3):155–68.
98. Jiang Y, Tsoi LC, Billi AC, Ward NL, Harms PW, Zeng C, et al. Cytokinocytes: the diverse contribution of keratinocytes to immune responses in skin. JCI Insight. 2020;5(20).
99. Morbe UM, Jorgensen PB, Fenton TM, von Burg N, Riis LB, Spencer J, et al. Human gut-associated lymphoid tissues (GALT); diversity, structure, and function. Mucosal Immunol. 2021;14(4):793–802.

100. Ruth MR, Field CJ. The immune modifying effects of amino acids on gut-associated lymphoid tissue. J Anim Sci Biotechnol. 2013;4(1):27.
101. Gunther J, Seyfert HM. The first line of defence: insights into mechanisms and relevance of phagocytosis in epithelial cells. Semin Immunopathol. 2018;40(6):555–65.
102. Mulder DJ, Pooni A, Mak N, Hurlbut DJ, Basta S, Justinich CJ. Antigen presentation and MHC class II expression by human esophageal epithelial cells: role in eosinophilic esophagitis. Am J Pathol. 2011;178(2):744–53.
103. Capasso D, Pepe MV, Rossello J, Lepanto P, Arias P, Salzman V, et al. Elimination of Pseudomonas aeruginosa through Efferocytosis upon Binding to Apoptotic Cells. PLoS Pathog. 2016;12(12): e1006068.
104. Moon S, Park Y, Hyeon S, Kim YM, Kim JH, Kim H, et al. Niche-specific MHC II and PD-L1 regulate CD4+CD8alphaalpha+ intraepithelial lymphocyte differentiation. J Exp Med. 2021;218(4).
105. Hatano R, Yamada K, Iwamoto T, Maeda N, Emoto T, Shimizu M, et al. Antigen presentation by small intestinal epithelial cells uniquely enhances IFN-gamma secretion from CD4+ intestinal intraepithelial lymphocytes. Biochem Biophys Res Commun. 2013;435(4):592–6.
106. Shenoy AT, Lyon De Ana C, Arafa EI, Salwig I, Barker KA, Korkmaz FT, et al. Antigen presentation by lung epithelial cells directs CD4(+) T(RM) cell function and regulates barrier immunity. Nat Commun. 2021;12(1):5834.
107. Axelrod ML, Cook RS, Johnson DB, Balko JM. Biological Consequences of MHC-II Expression by Tumor Cells in Cancer. Clin Cancer Res. 2019;25(8):2392–402.
108. Gkountidi AO, Garnier L, Dubrot J, Angelillo J, Harle G, Brighouse D, et al. MHC Class II Antigen Presentation by Lymphatic Endothelial Cells in Tumors Promotes Intratumoral Regulatory T cell-Suppressive Functions. Cancer Immunol Res. 2021;9(7):748–64.
109. Koyama M, Kuns RD, Olver SD, Raffelt NC, Wilson YA, Don AL, et al. Recipient nonhematopoietic antigen-presenting cells are sufficient to induce lethal acute graft-versus-host disease. Nat Med. 2011;18(1):135–42.
110. Saada JI, Pinchuk IV, Barrera CA, Adegboyega PA, Suarez G, Mifflin RC, et al. Subepithelial myofibroblasts are novel nonprofessional APCs in the human colonic mucosa. J Immunol. 2006;177(9):5968–79.
111. Jafari N, Khajenabi F, Masumi N, Abediankenari S, Ranjbaran H. Evaluation of HLA-DR and HLA-DQ expression in gastric cancer tissues. J Cancer Res Ther. 2024;20:204–10.
112. Heuberger C, Pott J, Maloy KJ. Why do intestinal epithelial cells express MHC class II? Immunology. 2021;162(4):357–67.
113. Ghasemi F, Tessier TM, Gameiro SF, Maciver AH, Cecchini MJ, Mymryk JS. High MHC-II expression in Epstein-Barr virus-associated gastric cancers suggests that tumor cells serve an important role in antigen presentation. Sci Rep. 2020;10(1):14786.
114. Thelemann C, Eren RO, Coutaz M, Brasseit J, Bouzourene H, Rosa M, et al. Interferon-gamma induces expression of MHC class II on intestinal epithelial cells and protects mice from colitis. PLoS ONE. 2014;9(1): e86844.
115. Sanderson IR, Bustin SA, Dziennis S, Paraszczuk J, Stamm DS. Age and diet act through distinct isoforms of the class II transactivator gene in mouse intestinal epithelium. Gastroenterology. 2004;127(1):203–12.
116. Mayer L, Eisenhardt D, Salomon P, Bauer W, Plous R, Piccinini L. Expression of class II molecules on intestinal epithelial cells in humans Differences between normal and inflammatory bowel disease. Gastroenterology. 1991;100(1):3–12.
117. Dotan I, Allez M, Nakazawa A, Brimnes J, Schulder-Katz M, Mayer L. Intestinal epithelial cells from inflammatory bowel disease patients preferentially stimulate CD4+ T cells to proliferate and secrete interferon-gamma. Am J Physiol Gastrointest Liver Physiol. 2007;292(6):G1630–40.
118. Koyama M, Mukhopadhyay P, Schuster IS, Henden AS, Hulsdunker J, Varelias A, et al. MHC Class II Antigen Presentation by the Intestinal Epithelium Initiates Graft-versus-Host Disease and Is Influenced by the Microbiota. Immunity. 2019;51(5):885–98 e7.
119. Westendorf AM, Bruder D, Hansen W, Buer J. Intestinal epithelial antigen induces CD4+ T cells with regulatory phenotype in a transgenic autoimmune mouse model. Ann N Y Acad Sci. 2006;1072:401–6.
120. Westendorf AM, Fleissner D, Groebe L, Jung S, Gruber AD, Hansen W, et al. CD4+Foxp3+ regulatory T cell expansion induced by antigen-driven interaction with intestinal epithelial cells independent of local dendritic cells. Gut. 2009;58(2):211–9.
121. Tian Y, Xu J, Li Y, Zhao R, Du S, Lv C, et al. MicroRNA-31 reduces inflammatory signaling and promotes regeneration in colon epithelium, and delivery of mimics in microspheres reduces colitis in mice. Gastroenterology. 2019;156(8):2281–96 e6.
122. Zhou W, Xu J, Wang C, Shi D, Yan Q. miR-23b-3p regulates apoptosis and autophagy via suppressing SIRT1 in lens epithelial cells. J Cell Biochem. 2019;120(12):19635–46.
123. Hou Q, Huang Y, Zhu S, Li P, Chen X, Hou Z, et al. MiR-144 Increases Intestinal Permeability in IBS-D Rats by Targeting OCLN and ZO1. Cell Physiol Biochem. 2017;44(6):2256–68.
124. Rawat M, Nighot M, Al-Sadi R, Gupta Y, Viszwapriya D, Yochum G, et al. IL1B Increases Intestinal Tight Junction Permeability by Up-regulation of MIR200C-3p. Which Degrades Occludin mRNA Gastroenterology. 2020;159(4):1375–89.
125. Ye D, Guo S, Al-Sadi R, Ma TY. MicroRNA regulation of intestinal epithelial tight junction permeability. Gastroenterology. 2011;141(4):1323–33.
126. Zhou Q, Costinean S, Croce CM, Brasier AR, Merwat S, Larson SA, et al. MicroRNA 29 targets nuclear factor-kappaB-repressing factor and Claudin 1 to increase intestinal permeability. Gastroenterology. 2015;148(1):158–69 e8.
127. Nakata K, Sugi Y, Narabayashi H, Kobayakawa T, Nakanishi Y, Tsuda M, et al. Commensal microbiota-induced microRNA modulates intestinal epithelial permeability through the small GTPase ARF4. J Biol Chem. 2017;292(37):15426–33.
128. Xiao HW, Li Y, Luo D, Dong JL, Zhou LX, Zhao SY, et al. Hydrogen-water ameliorates radiation-induced gastrointestinal toxicity via MyD88's effects on the gut microbiota. Exp Mol Med. 2018;50(1): e433.
129. Deguine J, Barton GM. MyD88: a central player in innate immune signaling. F1000 Prime Rep. 2014;6:97.
130. Li ZL, Lv LL, Tang TT, Wang B, Feng Y, Zhou LT, et al. HIF-1alpha inducing exosomal microRNA-23a expression mediates the cross-talk between tubular epithelial cells and macrophages in tubulointerstitial inflammation. Kidney Int. 2019;95(2):388–404.
131. Swamynathan SK. Kruppel-like factors: three fingers in control. Hum Genomics. 2010;4(4):263–70.
132. Suzuki T, Nishi T, Nagino T, Sasaki K, Aizawa K, Kada N, et al. Functional interaction between the transcription factor Kruppel-like factor 5 and poly(ADP-ribose) polymerase-1 in cardiovascular apoptosis. J Biol Chem. 2007;282(13):9895–901.
133. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, et al. The role of Tumor Necrosis Factor Alpha (TNF-alpha) in autoimmune disease and current TNF-alpha inhibitors in therapeutics. Int J Mol Sci. 2021;22(5).
134. Walsh MC, Lee J, Choi Y. Tumor necrosis factor receptor- associated factor 6 (TRAF6) regulation of development, function, and homeostasis of the immune system. Immunol Rev. 2015;266(1):72–92.
135. Deenick EK, Pelham SJ, Kane A, Ma CS. Signal Transducer and Activator of Transcription 3 Control of Human T and B Cell Responses. Front Immunol. 2018;9:168.
136. Zhang L, Kuca K, You L, Zhao Y, Musilek K, Nepovimova E, et al. Signal transducer and activator of transcription 3 signaling in tumor immune evasion. Pharmacol Ther. 2022;230: 107969.
137. Chen G, Shi Y, Zhang Y, Sun J. CircRNA_100782 regulates pancreatic carcinoma proliferation through the IL6-STAT3 pathway. Onco Targets Ther. 2017;10:5783–94.
138. Kwan HY, Liu B, Huang C, Fatima S, Su T, Zhao X, et al. Signal transducer and activator of transcription-3 drives the high-fat diet-associated prostate cancer growth. Cell Death Dis. 2019;10(9):637.
139. Riethmueller S, Ehlers JC, Lokau J, Dusterhoft S, Knittler K, Dombrowsky G, et al. Cleavage Site Localization Differentially Controls Interleukin-6 Receptor Proteolysis by ADAM10 and ADAM17. Sci Rep. 2016;6:25550.
140. Wolf J, Rose-John S, Garbers C. Interleukin-6 and its receptors: a highly regulated and dynamic system. Cytokine. 2014;70(1):11–20.
141. Sobah ML, Liongue C, Ward AC. SOCS Proteins in Immunity, Inflammatory Diseases, and Immune-Related Cancer. Front Med (Lausanne). 2021;8: 727987.
142. Cheng X, Zhang X, Su J, Zhang Y, Zhou W, Zhou J, et al. miR-19b downregulates intestinal SOCS3 to reduce intestinal inflammation in Crohn's disease. Sci Rep. 2015;5:10397.

143. Liu Z, Jiang J, Yang Q, Xiong Y, Zou D, Yang C, et al. MicroRNA-682-mediated downregulation of PTEN in intestinal epithelial cells ameliorates intestinal ischemia-reperfusion injury. Cell Death Dis. 2016;7(4): e2210.
144. Liu F, Wang X, Geng H, Bu HF, Wang P, De Plaen IG, et al. Interferon-gamma inhibits sirtuin 6 gene expression in intestinal epithelial cells through a microRNA-92b-dependent mechanism. Am J Physiol Cell Physiol. 2020;318(4):C732–9.
145. Chen Y, Du J, Zhang Z, Liu T, Shi Y, Ge X, et al. MicroRNA-346 mediates tumor necrosis factor alpha-induced downregulation of gut epithelial vitamin D receptor in inflammatory bowel diseases. Inflamm Bowel Dis. 2014;20(11):1910–8.
146. Shen J, Yan J, Wang Q, Zhuang L, Luo Y. MicroRNA-541-5p REgulates Type II Alveolar Epithelial Cell Proliferation and Activity by Modulating the HMGB1 Expression. Shock. 2022;57(4):536–43.
147. Giridhar PV, Bell SM, Sridharan A, Rajavelu P, Kitzmiller JA, Na CL, et al. Airway Epithelial KIF3A Regulates Th2 Responses to Aeroallergens. J Immunol. 2016;197(11):4228–39.
148. Wang C, Shan L, Qu S, Xue M, Wang K, Fu F, et al. The Coronavirus PEDV Evades Type III Interferon Response Through the miR-30c-5p/SOCS1 Axis. Front Microbiol. 2020;11:1180.
149. Hu X, Li J, Fu M, Zhao X, Wang W. The JAK/STAT signaling pathway: from bench to clinic. Signal Transduct Target Ther. 2021;6(1):402.
150. Zhang Q, Huang C, Yang Q, Gao L, Liu HC, Tang J, et al. MicroRNA-30c Modulates Type I IFN Responses To Facilitate Porcine Reproductive and Respiratory Syndrome Virus Infection by Targeting JAK1. J Immunol. 2016;196(5):2272–82.
151. Aguilar C, Costa S, Maudet C, Vivek-Ananth RP, Zaldivar-Lopez S, Garrido JJ, et al. Reprogramming of microRNA expression via E2F1 downregulation promotes Salmonella infection both in infected and bystander cells. Nat Commun. 2021;12(1):3392.
152. Izar B, Mannala GK, Mraheil MA, Chakraborty T, Hain T. microRNA response to Listeria monocytogenes infection in epithelial cells. Int J Mol Sci. 2012;13(1):1173–85.
153. Zeiner GM, Norman KL, Thomson JM, Hammond SM, Boothroyd JC. Toxoplasma gondii infection specifically increases the levels of key host microRNAs. PLoS ONE. 2010;5(1): e8742.
154. Nakamura S, Horie M, Daidoji T, Honda T, Yasugi M, Kuno A, et al. Influenza A Virus-Induced Expression of a GalNAc Transferase, GALNT3, via MicroRNAs Is Required for Enhanced Viral Replication. J Virol. 2016;90(4):1788–801.
155. Yang K, Wu M, Li M, Li D, Peng A, Nie X, et al. miR-155 suppresses bacterial clearance in Pseudomonas aeruginosa-induced keratitis by targeting Rheb. J Infect Dis. 2014;210(1):89–98.
156. Lu D, Chatterjee S, Xiao K, Riedel I, Wang Y, Foo R, et al. MicroRNAs targeting the SARS-CoV-2 entry receptor ACE2 in cardiomyocytes. J Mol Cell Cardiol. 2020;148:46–9.
157. Wicik Z, Eyileten C, Jakubik D, Simoes SN, Martins DC, Jr., Pavao R, et al. ACE2 Interaction networks in COVID-19: a physiological framework for prediction of outcome in patients with cardiovascular risk factors. J Clin Med. 2020;9(11).
158. Li C, Wang R, Wu A, Yuan T, Song K, Bai Y, et al. SARS-COV-2 as potential microRNA sponge in COVID-19 patients. BMC Med Genomics. 2022;15(Suppl 2):94.
159. Pepe G, Guarracino A, Ballesio F, Parca L, Ausiello G, Helmer-Citterich M. Evaluation of potential miRNA sponge effects of SARS genomes in human. Noncoding RNA Res. 2022;7(1):48–53.
160. Gheware A, Ray A, Rana D, Bajpai P, Nambirajan A, Arulselvi S, et al. ACE2 protein expression in lung tissues of severe COVID-19 infection. Sci Rep. 2022;12(1):4058.
161. Chen Q, Zhang F, Dong L, Wu H, Xu J, Li H, et al. SIDT1-dependent absorption in the stomach mediates host uptake of dietary and orally administered microRNAs. Cell Res. 2021;31(3):247–58.
162. Li J, Zhang Y, Li D, Liu Y, Chu D, Jiang X, et al. Small non-coding RNAs transfer through mammalian placenta and directly regulate fetal gene expression. Protein Cell. 2015;6(6):391–6.
163. Zhang L, Hou D, Chen X, Li D, Zhu L, Zhang Y, et al. Exogenous plant MIR168a specifically targets mammalian LDLRAP1: evidence of cross-kingdom regulation by microRNA. Cell Res. 2012;22(1):107–26.
164. Zhou Z, Li X, Liu J, Dong L, Chen Q, Liu J, et al. Honeysuckle-encoded atypical microRNA2911 directly targets influenza A viruses. Cell Res. 2015;25(1):39–49.
165. Izumi H, Tsuda M, Sato Y, Kosaka N, Ochiya T, Iwamoto H, et al. Bovine milk exosomes contain microRNA and mRNA and are taken up by human macrophages. J Dairy Sci. 2015;98(5):2920–33.
166. Manca S, Upadhyaya B, Mutai E, Desaulniers AT, Cederberg RA, White BR, et al. Milk exosomes are bioavailable and distinct microRNA cargos have unique tissue distribution patterns. Sci Rep. 2018;8(1):11321.
167. Aquilano K, Ceci V, Gismondi A, De Stefano S, Iacovelli F, Faraonio R, et al. Adipocyte metabolism is improved by TNF receptor-targeting small RNAs identified from dried nuts. Commun Biol. 2019;2:317.
168. Cavalieri D, Rizzetto L, Tocci N, Rivero D, Asquini E, Si-Ammour A, et al. Plant microRNAs as novel immunomodulatory agents. Sci Rep. 2016;6:25761.
169. Liang G, Zhu Y, Sun B, Shao Y, Jing A, Wang J, et al. Assessing the survival of exogenous plant microRNA in mice. Food Sci Nutr. 2014;2(4):380–8.
170. Teng Y, Xu F, Zhang X, Mu J, Sayed M, Hu X, et al. Plant-derived exosomal microRNAs inhibit lung inflammation induced by exosomes SARS-CoV-2 Nsp12. Mol Ther. 2021;29(8):2424–40.
171. Zhou LK, Zhou Z, Jiang XM, Zheng Y, Chen X, Fu Z, et al. Absorbed plant MIR2911 in honeysuckle decoction inhibits SARS-CoV-2 replication and accelerates the negative conversion of infected patients. Cell Discov. 2020;6(1):54.
172. Hou D, He F, Ma L, Cao M, Zhou Z, Wei Z, et al. The potential atheroprotective role of plant MIR156a as a repressor of monocyte recruitment on inflamed human endothelial cells. J Nutr Biochem. 2018;57:197–205.
173. Teng Y, Ren Y, Sayed M, Hu X, Lei C, Kumar A, et al. Plant-Derived Exosomal MicroRNAs Shape the Gut Microbiota. Cell Host Microbe. 2018;24(5):637–52 e8.
174. Tong L, Hao H, Zhang X, Zhang Z, Lv Y, Zhang L, et al. Oral Administration of Bovine milk-derived extracellular vesicles alters the gut microbiota and enhances intestinal immunity in mice. Mol Nutr Food Res. 2020;64(8): e1901251.
175. Huang H, Davis CD, Wang TTY. Extensive degradation and low bioavailability of orally consumed corn miRNAs in mice. Nutrients. 2018;10(2).
176. Mico V, Martin R, Lasuncion MA, Ordovas JM, Daimiel L. Unsuccessful detection of plant MicroRNAs in beer, extra virgin olive oil and human plasma after an acute ingestion of extra virgin olive oil. Plant Foods Hum Nutr. 2016;71(1):102–8.
177. Snow JW, Hale AE, Isaacs SK, Baggish AL, Chan SY. Ineffective delivery of diet-derived microRNAs to recipient animal organisms. RNA Biol. 2013;10(7):1107–16.
178. Zhao Q, Mao Q, Zhao Z, Dou T, Wang Z, Cui X, et al. Prediction of plant-derived xenomiRs from plant miRNA sequences using random forest and one-dimensional convolutional neural network models. BMC Genomics. 2018;19(1):839.
179. Nunes S, Bastos R, Marinho AI, Vierira R, Benicio I, de Noronha MA, et al. Recent advances in the development and clinical application of miRNAs in infectious diseases. Non-coding RNA Res. 2025;10:41–54.
180. van der Ree MH, de Vree JM, Stelma F, Willemse S, van der Valk M, Rietdijk S, et al. Safety, tolerability, and antiviral eff ect of RG-101 in patients with chronic hepatitis C: a phase 1B, double-blind, randomised controlled trial. Lancet. 2016;389(10070):709–17.
181. Rheault M, Cousineau SE, Fox DR, Abram QH, Sagan SM. Elucidating the distinct contributions of miR-122 in the HCV life cycle reveals insights into virion assembly. Nucleic Acids Res. 2023;51(5):2447–63.
182. Stelma F, van der Ree MH, Sinnige MJ, Brown A, Swadling L, de Vree ML. Immune phenotype and function of natural killer and t cells in chronic hepatitis C patients who received a single dose of anti-microrna-122, RG-101. Hepatol. 2017;66(1).
183. Nakao K, Miyaaki H, Ichikawa T. Antitumor function of microRNA-122 against hepatocellular carcinoma. J Gastroenterol. 2014;49:589–93.
184. van Zandwijk N, Pavlakis N, Kao SC, Linton A, Boyer MJ, Clarke S, et al. Safety and activity of microRNA-loaded minicells in patients with recurrent malignant pleural mesothelioma: a first-in-man,

phase 1, open-label, dose-escalation study. Lancet Oncol. 2017;18(10):1386–96.
185. Mutsaers SE. The mesothelial cell. Int J Biochem Cell Biol. 2004;36:9–16.
186. Ramos-Nino ME, Testa JR, Altomare DA, Pass HI, Carbone M, Bocchetta M, et al. Cellular and Molecular Parameters of Mesothelioma. J Cell Biochem. 2006;98(4):723–34.
187. Reid G, Johnson TG, van Zandwijk N. Manipulating microRNAs for the treatment of malignant pleural mesothelioma: past, present and future. Front Oncol. 2020;10.
188. Hong DS, Kang YK, Borad M, Sachdev J, Ejadi S, Lim Y, et al. Phase 1 study of MRX34, a liposomal miR-34a mimic, in patients with advanced solid tumours. British J Cancer. 2020;122:1630–7.